Review

One year in review 2018: progress in osteoporosis treatment

A. Figliomeni, V. Signorini, M. Mazzantini

[1]*Rheumatology Unit, Department of Medicine, University of Pisa, Italy.*

Antonio Figliomeni, MD
Viola Signorini, MD
Maurizio Mazzantini, MD, PhD

Please address correspondence to:
Dr Maurizio Mazzantini,
Reumatologia,
Dipartmento di Medicina
Clinica Sperimentale,
Università di Pisa,
Via Roma 67,
56100 Pisa, Italy.
E-mail: mmazzant@int.med.unipi.it

Received on August 7, 2018; accepted in revised form on October 9, 2018.

Clin Exp Rheumatol 2018; 36: 948-958.

Key words: osteoporosis, teriparatide, romosozumab, abaloparatide, glucocorticoid induced osteoporosis

Competing interests: none declared.

ABSTRACT

Osteoporosis is a generalised bone disease characterised by decreased bone mass and deterioration of bone microarchitecture predisposing to fragility fractures. Bone fractures are a remarkable social and economic health problem, and several studies have been carried out in order to reduce their occurrence. Inhibiting bone resorption and increasing bone formation are the mainstay of treatment, anti-catabolic and anabolic, respectively. This review highlights the most recent advances in osteoporosis and reports the evidence of efficacy and safety of anabolic treatment of osteoporosis, as evaluated by randomised, controlled trials published during 2017. As the most common form of secondary osteoporosis, we will also discuss the 2017 state-of-the-art on pathogenesis and treatment of glucocorticoid-induced osteoporosis.

Introduction

Osteoporosis (OP) is a generalised bone disease characterised by decreased bone mass and deterioration of bone microarchitecture resulting in increased fracture risk (1). Aetiology of the disease is related to genetic, environmental, and lifestyle factors; in particular, the most important risk factors are low body mass index, inactivity, low dietary calcium intake, D-vitamin deficiency, smoke, chronic therapy with glucocorticoids, and a genetic background. Primary OP is defined when occurring after menopause (postmenopausal OP) or with advanced age (senile OP) without any identifiable cause. Secondary OP is caused by a number of diseases and drugs. Bone mass density (BMD) is the only parameter of bone strength that we can measure precisely and accurately by means of bone densitometry. According to the World Health Organisation (WHO) (2) a diagnosis of OP should be based on BMD measured by dual-energy x-ray absorptiometry (DXA), compared to the mean BMD of young normal adults of the same sex (peak bone mass). On the basis of the standard deviation (SD) above or below the mean peak bone mass (T-score), it has been reported that fracture risk begins to increase exponentially at a T-score <-2.5 SD, which has been established by the WHO as the cut-off for diagnosing OP. However, the diagnosis of OP should be confirmed by a thorough physical, clinical, and laboratory evaluation. Furthermore, a diagnosis of OP is made when a patient has any fragility fracture occurring after a low trauma or even with no trauma at all, as after a fall from the standing position.

OP is a major health problem. Over 200 million individuals suffer from the disease and 9 million new osteoporotic fractures occur every year (3). Approximately 3.5 million women and 1 million men have OP in Italy (4). The incidence of OP increases with ageing, affecting most of the population after the eighth decade of life. Common sites of osteoporotic fracture are spine, hip, distal forearm and proximal humerus. The lifetime risk of any osteoporotic fracture is very high, from 40 to 50% in women and from 13 to 22% for men at the age of 50 years (5, 6). The number of hip fractures in the Italian population aged 65 years or older is approximately 100,000 per year, while the estimated incidence of vertebral fractures is 155,000 per year (7). Vertebral fractures are associated with an increased risk of further vertebral fractures with an incidence of 19.2% in the first year after the previous event (8). This is a remarkable problem because it has been reported that more than two thirds of vertebral fractures are not diagnosed, which delays an effective anti-osteoporotic treatment (9). Osteoporotic fractures have important social

and economic implications besides the health burden: the 1-year mortality rate for patients with a fracture of the proximal femur is about 30% (10). Osteoporotic fractures are one of the leading causes of death among the elderly, with an incidence comparable to that from stroke and breast cancer, and 4-fold that from endometrial cancer (4). Collectively, all osteoporotic fractures account for 2.7 million fractures in men and women in Europe at a direct cost, in 2010, of €37 billion in the 27 EU countries (11).

We will here provide an overview of the most recent advances in OP, with special regard to its pathogenesis and new efforts to cure the disease with an expanding class of treatment, as evaluated by randomised, controlled trial published during 2017: the bone anabolic therapy. To a better understanding of the mechanisms of action of anabolic treatment, we will briefly review also recent developments in the field of bone biology. As the most common form of secondary osteoporosis, we will discuss the 2017 state-of-the-art of pathogenesis and treatment of glucocorticoid-induced OP.

Novel insights into bone biology

During life, bone undergoes modelling and remodelling. Bone modelling is the process by which bones change shape or size in order to respond to physiologic stimuli or mechanical forces which skeleton is submitted to; bone modeling occurs during birth to adulthood and is responsible for gain in skeletal mass and changes in skeletal form. Bone remodelling is the replacement of old tissue by new bone tissue so that bone can maintain its strength and properties. Bone remodelling is a life-long process. The main cells involved in bone remodelling are osteoblasts and osteoclasts. These cells are tightly coupled: their cooperative functions lead to resorption of old damaged bone and formation of new bone sequentially. Other cells are involved in bone remodeling, such as the osteocytes that act as mechanosensors and endocrine cells, and the bone lining cells (12).

The most relevant pathways involved in bone modelling/remodelling are: Wnt/βcatenin, sclerostin, insulin growth factor 1 (IGF-1), and glucagone-like-peptide 1 (GLP-1). In the last years several studies have demonstrated the central role of Wnt/βcatenin in bone (13). Wnt/βcatenin signalling is activated by binding of Wnt proteins to receptor complexes composed of frizzled receptors and co-receptors of the low density lipoprotein receptor-related protein (LRP) family, LRP5 and 6. This event stabilises intracellular β catenin, which moves to the nucleus, and promotes gene transcription. This way increases the differentiation of mesenchymal stem cells toward osteoblasts and increases maturation and survival of osteoblasts and osteocytes; moreover, Wnt signal inhibits osteoclast generation by increasing the expression in osteoblasts and osteocytes of osteoprotegerin (OPG), a decoy receptor of the receptor activator of Nfκb ligand (RANKL) (14). A potent antagonist of Wnt signalling is sclerostin (15). This is a protein encoded by the SOST gene and it is secreted by the osteocytes. Sclerostin binds to the Wnt co-receptors LRP5 preventing the nuclear translocation of βcatenin. Sclerostin also interacts with LRP4, another member of the LRP family of proteins, which is required for the inhibitory action of sclerostin on Wnt/βcatenin signalling (16). Parathyroid hormone (PTH) reduces sclerostin expression; this action seems to contribute to the anabolic actions of PTH in the skeleton. It has been observed that serum levels of sclerostin do not correlate with changes in bone mineral density (BMD) in patients with OP, therefore its diagnostic value is limited (17).

IGF-1 is a peptide that acts as a systemic and local regulator of skeletal growth (18). In bone cells, the synthesis of IGF-1 is primarily dependent on PTH, and IGF-1 is required to obtain an anabolic response to PTH. IGF-1 promotes the osteoblast activity and inhibits osteoblast apoptosis. IGF-1 increases osteoblast differentiation indirectly by stabilising β-catenin and enhancing Wnt signalling. IGF-1 regulates also osteoclasts activity increasing the synthesis of RANKL (19). Many studies have also demonstrated that the IGF-1 signalling pathway is one of the key factors in the cellular response to mechanical stimuli but the details remain to be elucidated (20, 21).

Further investigations have indicated that GLP-1 acts on bone tissue by promoting bone formation and inhibiting bone resorption (22). GLP-1 might bind to its receptor on osteoblast and its function is possibly mediated by protein kinase pathways or Wnt pathways. GLP-1 increases osteoblast number, promotes the expression of genes related to bone formation and increases serum level of bone formation markers. GLP-1 also promotes mesenchymal stem cell differentiation from adipocytes toward osteoblasts. On the other hand GLP-1 decreases osteoclast number and serum level of bone resorption markers. However, the specific molecular mechanisms responsible for these effects have still not been fully elucidated (22).

Osteocyte as mechano-sensors

Osteocytes are osteoblasts that remain surrounded by the newly formed osteoid, which later in time becomes calcified bone. Osteocytes situated deep in bone matrix maintain contact with newly incorporated osteocytes, and with osteoblasts and bone lining cells on the bone surfaces, through an extensive network of cell processes (the so-called osteocytes canalicular network). They respond to changes in physical forces upon bone and transduce messages to cells on the bone surface, directing them to initiate resorption or formation (23). Osteoblasts are activated when load is increased, while osteoclasts are partially suppressed; conversely, if load is reduced (24). Several stressors have been evaluated as mechanical stimuli: fluid flow shear stress, hydrostatic pressure and bone matrix deformation (25). It is already unknown how osteocytes receive these mechanical stimuli: it seems that distinct elements are involved in this process, such as integrins, calcium channels and G-protein coupled receptors. Once the signal is sensed by osteocytes, it is transduced through biological ways. In this process are involved several pathways such as: intracellular calcium, ATP, nitrogen oxide, prostaglandin and Wnt (26).

The final effect is the expression of effectors, including SOST and RANKL. Mechano-transduction is a process that becomes less efficient with age. Recent studies have demonstrated that osteocytes morphology, number and density change with age and this could be related to an impaired ability to respond to mechanical stimuli and to maintain integrity of bone mass and architecture with aging (27, 28).

Glucocorticoid-induced OP

Glucocorticoid-induced OP (GIOP) is the most frequent type of secondary OP. It has been estimated that glucocorticorticoids (GCs) are used by 0.5 to 0.9% of the general population and up to 2.5% of patients older than 70 years (29). GCs negatively affect bone through loss of bone mass and profound changes in its microarchitecture and strength. GIOP is associated with a high prevalence of vertebral fractures, because the effects of GCs involve mainly the trabecular bone. A multicentric cross-sectional study showed that 37% of patients under chronic therapy (at least 6 months) with GCs have at least one vertebral fracture (45% in patients older than 70 years) (30). According to a retrospective study (31), the relative risk of vertebral fractures in patients treated with GCs compared to patient not exposed to GCs was 2.6 (95% CI, 2.31–2.92). Furthermore, similar trend was found among non-vertebral fractures (RR 1.33; 95% CI, 1.29–1.38) and hip fractures (RR 1.61; 95% CI, 1.47–1.76). There is a direct relationship between the daily-dose of GCs and the risk of vertebral fractures (RR 1.55 in patients treated with doses lower than 2.5 mg of prednisone and 5.18 for doses up to 7.5 mg). These data showed that the risk of vertebral fractures increases even with very low daily doses, as small as 2.5 mg. Because GCs determine changes in bone quality, not only in bone mass, there is not a linear relationship between BMD reduction as assessed by DXA and the risk of fracture (32). GCs affect bone through different mechanisms: they induce reduction in bone formation, increase of bone resorption and also exert indirect effects that determine increased fracture risk. GCs have been shown to suppress osteoblast differentiation by stimulating transcription and release of Wnt pathway inhibitors, such as dickkopf-1 (Dkk-1), sclerostin and glycogen synthase kinase-3 (33, 34). GCs impair osteoblast function through other pathways: they promote apoptosis of osteoblasts by activating caspase-3 (35). GCs also stimulate the bone marrow stromal cells to differentiate towards adipocytes instead of osteoblasts by up-regulation of the peroxisome proliferator-activated receptor-γ2 (PPARγ-2) and the Runt-related transcription factor 2 (Runx2) (36, 37). Inhibition of osteoblasts leads to impaired biosynthesis of type I collagen, the predominant organic component of the bone matrix (38). Bone strength is reduced also by the increased apoptosis of osteocytes induced by GCs: the reduction of osteocytes number impairs signalling from the osteocyte-canalicular network, which ultimately affects bone strength because of failure to respond with local remodelling to bone damage (35). The effect of GCs on bone resorption is less clear than that on bone formation. In the early use of GCs there is a rapid increased of bone loss, that lasts 3–6 months after the start of treatment (39) and is probably due to the effect of GCs on osteoclast: by acting on the Wnt-signalling pathway, GCs induce up-regulation of RANKL expression and suppression of OPG (40, 41). The main indirect effect of GCs on bone is the impairment of calcium metabolism. GCs lower intestinal absorption of calcium by inhibiting vitamin D action and by down-regulate the expression of calcium receptors in the duodenum. Furthermore, GCs down-regulate the expression of tubular calcium receptors in the kidneys. Low calcium intestinal absorption may lead to increased plasmatic levels of PTH. Another negative indirect effect of GCs on bone remodelling is the influence on the hypothalamus–pituitary–adrenal-axis (42). GCs reduce synthesis and release of gonadotropin-releasing hormone and inhibit synthesis and release of luteinising hormone and follicle-stimulating hormone at the hypothalamus level. Therefore, GCs induce modulation of steroidogenesis and gametogenesis on the testis and ovary (42). Another important negative effect of GCs is the increased risk of falls because of decreased balance, due to muscle hypotrophy that is caused by muscle proteolysis, in particular through the activation of the ubiquitin proteasome and the lysosomal systems, and reduced protein synthesis by inhibition of IGF and by stimulating the muscle to produce myostatin, which inhibits myogenesis (43).

Anabolic treatment of OP

The improved understanding how osteoblasts and osteoclasts functions are coupled by systemic and local factors has led years ago to the use of the first anabolic therapy of OP: teriparatide (TRPT). Moreover, over last two years, two other anabolic drugs have been investigated with regard to their efficacy in reducing fractures and increasing bone mass: Abaloparatide (ABL) and Romosozumab (ROMO). Here we summarise the most relevant data about these drugs, as in 2017.

Teriparatide

TRPT is the N-teminal 1-34 amino-acid fragment of the recombinant human parathyroid hormone which is an analogous of PTH. TRPT binds to the same receptor of PTH, expressed in osteoblasts and osteoclast precursors. The primary target cell for PTH in bone is the osteoblast/osteocyte. Here, PTH binds to Type 1 PTH receptor (PTHR1), a class II G-protein coupled receptor that activates several intracellular signal pathways. Early pre-clinical studies showed that the intermittent binding of PTH to its receptor PTHR1 was able to increase bone anabolism, whereas continuous stimulation promoted bone resorption (44). It has been shown that binding of PTH with its receptor increases the differentiation of mesenchymal cells into osteoblasts, enhances osteoblast maturation, proliferation and activity and inhibits osteoblast apoptosis. In the latest years, various studies suggested that the anabolic effect of intermittent PTH and its analogous is mediated by Wnt signalling (45). Finally, intermittent PTH stimulates bone formation by reducing SOST/sclerostin

expression in osteocytes (46). On the other hand, PTH improves expression of RANKL, which activates and stimulates osteoclasts. The short exposure of bone to PTH, or PTH analogous, instead of continuous exposure, lead to a temporary dissociation between bone formation and resorption, with an overall anabolic effect on bone. The use of TRPT is limited to 2 years because of the development of osteosarcoma in pre-clinical animal studies (47, 48) and the decrease of its anabolic effect (49).

TRPT is indicated, at the dose of 20 μg daily, for the treatment of postmenopausal women with OP who are at high risk of fracture (50), to increase bone mass in men with primary or hypogonadal OP who are at high risk of fracture (51) and finally to improve bone mass in GIOP (52). Several OP treatment guidelines, mainly in Europe, recommend the use of TRPT for the treatment of severe OP as a second-line treatment. Thus, many patients who use TRPT have been previously treated with antiresorptives. For this reason, it is important to know whether TRPT has the same efficacy in these patients as compared to patients who have never received any treatment. Preclinical studies in ovariectomised rats observed that TRPT significantly increases bone mass and bone strength regardless of previous therapies (53). Using data from the European Study of Forsteo (EUROFORS) (54), the effects of 2 years TRPT on women previously treated with antiresorptive drugs for at least one year were analysed (50): the response to TRPT, as measured by BMD changes over time, was not modified neither by previous antiresorptive therapy nor the lag time between previous therapy and TRTP even if BMD increases were less in patients previously treated with bisphosphonates than in the treatment-naive group. Another study (55) evaluated 1,433 individuals (679 naïve and 774 pre-treated with bisphophonates): the results showed that BMD increased significantly at 24 months in both groups of subjects. The incidence rates of new vertebral and non-vertebral fractures at 24 months were 1.69% and 3.37%, respectively, in treatment-naive patients and 3.60% and 5.56%, respectively, in bisphosphonate-pretreated patients.

Many studies have evaluated the effect of TRPT together with antiresorptive agents, with the rationale that both stimulation of bone formation and inhibition of bone resorption would be more effective than either approach alone. Results from the concomitant use of bisphosphonates and TRPT were mixed. A combination of alendronate with TRPT did not show a superior effect on BMD (56, 57). The combination of zoledronic acid and TRPT led to faster increase in lumbar and hip BMD than the respective drug alone until 26 weeks. Instead, after 52 weeks, lumbar BMD in the TRPT group and hip BMD in the zoledronic acid group were similar to those observed in the combination group (58). In contrast, there are studies that have demonstrated that the combination of denosumab and TRPT produced a more significant effect on BMD than each drug did alone. A Japanese study enrolled 30 treatment-naive postmenopausal osteoporotic women who were randomly divided in two groups: only denosumab group, and combination group. After two years, it has been observed that lumbar vertebrae BMD increased more in combination group than denosumab alone (17.2% increase *vs.* 9.6%, $p<0.05$) (59). Similar results were by an Italian study (60). Also, the Denosumab And TRPT Administration (DATA) study (61) showed that the combination of denosumab and TRPT was superior than each drug alone. In this study, 94 postmenopausal women were randomised to receive TRPT, denosumab 60 mg every 6 months, or both; BMD was measured after 1 year. Lumbar spine BMD increased more in combination group than in TRPT ($p=0.0139$) or denosumab ($p=0.0005$); same result has been observed in femoral neck ($p=0.0007$ and $p=0.0238$, respectively) and total hip BMD ($p=0.0001$ and $p=0.0011$, respectively). DATA extension study (62) observed same results after 2 years. More recently, the DATA High Resolution peripheric QCT study (63) showed that the combination of denosumab and TRPT produced a more prominent effect on bone microarchitecture than each drug did alone. Total volumetric bone mineral density (vBMD) at the radius and tibia, trabecular vBMD at the radius, and cortical vBMD at the tibia all increased more in the combination group than in monotherapy groups ($p<0.002$ for all comparisons). Also cortical thickness at the tibia increased more in the combination group ($p<0.001$).

Since interruption of TRPT leads to a decline in BMD, it is crucial to use an anti-resorptive agent at the end of the 2-years TRPT in order to maintain BMD. In the DATA switch study (64), women originally assigned to 2 years of TRPT received 2 years of denosumab, whereas subjects who originally received 2 years of denosumab were treated with 2 years of TRPT; subjects who originally received both drugs, were treated with 2 years of denosumab alone. In women switching from TRPT to denosumab, total hip BMD continued to improve (6.6±3.3% at 48 month). In women switching from combination therapy to denosumab, total hip BMD also increased (8.6±3.0% at 48 month). In women who received 24-months of denosumab followed by 24-months of TRPT, total hip BMD was progressively reduced from 24 to 36 months before beginning to increase between 36 and 42 months. This study indicated that TRPT treatment after denosumab was associated with temporary bone loss in lumbar spine and proximal femur and with prolonged BMD decrease in distal radius; conversely, TRPT followed by denosumab further increased BMD of lumbar spine and proximal femur. It is well established that at the end of TRPT therapy antiresorptive treatment can increase the beneficial effect of anabolic therapy, but which antiresorptive drug is more useful? A study compared the effect on BMD of switching daily TRPT to oral bisphosphonates or to denosumab in patients with primary OP (65). After 12 months, the increase in BMD was significantly greater in the switch-to-denosumab group compared to the switch-to-bisphosphonates group: lumbar spine +6.2 *vs.* +2.6%, $p<0.01$; total hip +4.2 *vs.* +1.1%, $p<0.05$; and femoral neck +3.5 *vs.* +1.4%, $p<0.05$. This result could be explained with the different mechanisms

of action of denosumab and bisphosphonates: bisphosphonates act only on mature osteoclasts inducing apoptosis of these cells (66), while denosumab inhibits not only mature osteoclasts, but also the RANKL-induced osteoclastogenesis from precursors (67). The DATA-follow up study (68) compared the rates of bone loss in postmenopausal women who discontinued denosumab or TRPT and received no additional drugs to women who received antiresorptive therapy. In the 22 women not receiving follow-up therapy, femoral neck, total hip, and spine BMD decreased by -4.2±4.3%, -4.5±3.6%, and -10.0±5.4%, respectively, while BMD was maintained in those who received follow-up antiresorptive drugs. Among untreated women, femoral neck BMD decreased more in those discontinuing denosumab (-5.8±4.0%) than in those discontinuing TRPT (-0.8±2.6%), this difference reaching statistical significance (p=0.008.) Total hip, but not spine BMD, showed a similar pattern.

The previous studies compared TRPT to antiresorptive agents evaluating their effects using surrogate markers of efficacy, such BMD and markers of bone turnover. The VERO study (69) on the effects of TRPT and risedronate on new fractures in post-menopausal women with severe osteoporosis compared the efficacy of these two drugs using the reduction of the fracture risk as the primary outcome. Postmenopausal OP women (n=1366) who had at least two moderate or one severe vertebral fracture were randomly and blindly assigned to TRPT or oral risedronate (35 mg weekly). The primary endpoint was the percentage of subjects with at least one new vertebral fracture during the 24-month study period. In TRPT group, new vertebral fractures occurred in 5.4% *vs*. 12% in the risedronate group (p<0.0001). In addition, clinical fractures and non-vertebral fragility fractures occurred in lower percentage in TRPT group compared to risedronate. It would be reasonable to assume that TRPT should be of first choice in treating osteoporotic postmenopausal women with severe OP.

A retrospective study observed the effects of TRPT versus ALN on radiographic outcomes in the treatment of osteoporotic vertebral fractures (70). Ninety-eight osteoporotic patients were treated with TRPT (n=38) or 35 mg of ALN weekly (n=60). The union rate of vertebral fractures at six months was 89% in the TRPT group and 68% in the ALN group (p=0.026). However, this difference may be merely due to the lower dose of alendronate than that considered effective in reducing fractures.

Abaloparatide

Abaloparatide (ABL) is a new anabolic drug recently approved by the Food and Drug Administration for postmenopausal women with OP and high risk of vertebral fractures (71). It is a synthetic 34 amino acids peptide that acts as agonist of Type 1 PTH receptor (PTHR1), resulting in increase of intracellular cAMP concentration (72). ABL has 41% homology to PTH 1-34 and 76% homology to PTH-related protein (PTHrP). While PTH has endocrine proprieties and is the principal regulator of the calcium homeostasis, PTHrP is a hormone with a preponderant paracrine action, which is very important in the endochondral bone development, the tooth eruption, and during formation of mammary glands. Preclinical and clinical studies has showed that ABL has a net anabolic effect in the bone metabolism, and, in comparison to TRPT, exerts a lesser stimulation of the catabolic metabolism. This difference is not completely understood, but one plausible explanation is the different interaction of PTH and PTHrP (and consequently of TRPT and ABL) with their receptor. PTHR1 presents two high affinity conformation, R0 and RG; it has been demonstrated that PTH binds R0 conformation while PTHrP has high affinity for the RG conformation. The activation of the first conformation of PTHR1 causes longer activation of the G-protein and persistent cAMP production. This stimulation, in particular in osteoclasts, is related to a more catabolic action and consequent increase in plasmatic calcium levels. Activation of the RG conformation of PTHR1 is related to a transient generation of cAMP and a consequent lesser catabolic effect and calcium mobilisation (72).

Studies on ABL took into account the effects on BMD, the effect on plasmatic levels of formation and resorption bone markers, the change of incidence of vertebral and non-vertebral fractures, and, finally, the safety profile. In a phase 2, randomised, double-blind, placebo-controlled trial (73), the efficacy of different doses of daily ABL was compared with TRPT and placebo for 24 weeks. This study showed that patients treated with ABL 80 μg daily or TRPT presented significant increase in BMD at all sites of measurement in comparison with placebo, while significant difference between ABL and TRPT was found in the BMD gain at total hip (+2.6% *vs*. +0.4%, p<0.05). The positive effect on BMD was confirmed also in the Abaloparatide Comparator Trial in Vertebral Endpoints (ACTIVE) (74), that is the first phase 3 randomised study on ABL. In particular, in comparison to patients treated with TRPT, patients treated with ABL showed greater increase of femoral and total hip BMD at 6, 12 and 18 months (p<0.001), and, at lumbar spine, BMD significantly increased at 6 and 12 months (p<0.001). Regarding changes of serum biochemical markers of bone formation (Procollagen type 1 amino-terminal propeptide, P1NP) and bone resorption (collagen type 1 cross-linked C-telopeptide, CTX), both studies showed a significant increase of P1PN in patients treated with ABL (with a linear trend with drug doses), while CTX levels were significantly higher in patients treated with TRPT, suggesting that TRPT stimulates bone resorption more than ABL (73, 74).

The ACTIVE study (74) had as primary end point the evaluation of incidence of vertebral fractures in 2463 postmenopausal women assigned to double-blinded ABL 80μg (n=821) or placebo (n=824), or open label TRPT (n=818) for 18 months. The main inclusion criteria were BMD T-scores ≤-2.0 and >-5.0 at the lumbar spine or femoral neck and radiological evidence of mild to moderate vertebral fractures, according the Genant's method (75), or a history of low-traumatic non-vertebral fracture within the past five years. At 18 months, among the patients in ABL group, 4 had

at least one vertebral fracture (0.6%) while placebo group reported fractures in 30 patients (4.2%). In comparison to placebo, ABL offered a risk difference (RD) of -3.64 (95% CI, -5.42 to -2.10) and a Relative Risk (RR) of 0.14 (95% CI, 0.05 to 0.39, $p<0.001$). Six patients treated with TRPT had new vertebral fractures (0.8%), with no statistical difference *vs*. ABL. Furthermore, the Kaplan-Meier estimated event rate for non-vertebral fractures at 18 months was significantly lower ($p=0.049$) in the ABL group (2.7%) as compared to the placebo group (4.7%) with a RD of -2.1 (95% CI, -4.2 to 0.00) and hazard ratio of 0.57 (95% CI, 0.32 to 1.00).

Adverse effects of ABL were mild and moderate. With regard to hypercalcaemia, in the phase 2 study (73) it was reported that patients treated with TRPT had significantly larger increase of blood calcium than both placebo and ABL groups. In a similar way, in the ACTIVE study (74) hypercalcaemia incidence in the ABL group (3.4%) was significantly lower than that of TRPT group (6.4%) ($p=0.006$) at any time point. Furthermore, measurements of serum calcium 4-hour after drug administration showed significantly lower incidence of hypercalcemia in ABL group (3.4%) than in the TRPT group (6.1%) ($p=0.01$).

Novel evidence on Abaloparatide

In 2017, five studies on ABL were published. Three of these papers (76-78) analysed cohorts of the ACTIVE study (74), one reported histologic changes in bone after treatment with ABL (79), and one described the incidence of osteosarcoma in rats chronically exposed to ABL (80).

As reported above, the ACTIVE trial compared the incidence of vertebral and non-vertebral fractures and the change of BMD in 2463 post-menopausal women treated with ABL 80 μg, TRPT or placebo for 18 months. The patients were stratified on the base of five risk factors, such as BMD measured at lumbar spine, femoral neck, and total hip, age, and prior fractures. In order to assess whether fracture risk reductions and BMD increases were consistent across different category of risk at baseline. The results showed no interactions between any level of baseline risk and the effect of ABL on new fractures on BMD changes. Thus, ABL was shown to be potentially useful for a broad group of women with OP (76). Moreover, in a post hoc analysis of the ACTIVE study, it was evaluated whether the efficacy of ABL on reducing the risk of bone fracture depends on the patients' baseline risk of fracture (77). The 10-year probability of bone fracture (81) (based on factors as age, weight, height, gender, GCs use, smoking history, alcohol use, fracture history, and rheumatoid arthritis affection) of patients treated with ABL and placebo was calculated retrospectively. Patients were divided in 5 percentiles according to the calculated 10-year risk of fractures. It was found that the reduction of the hazard ratios of fractures with ABL was not significantly associated to the fracture probability. Thus, the efficacy of ABL to decrease the risk of major osteoporotic fractures or any clinical fracture in postmenopausal women with OP appears independent of baseline fracture probability.

Data from the ACTIVE study were also used in the ACTIVExtend study (78). Patients treated for 18 months with ABL or placebo, after a pause of 1 month, were given blinded administration of ABL or placebo or open-blinded addition of weekly 70 mg Alendronate (ALN) for 6 extra months. At the end of the observation period of the ACTIVE + ACTIVExtend (18 + 6 months), treatment with ABL + ALN was associated with a cumulative incidence of new morphometric vertebral fractures of 0.55%, which was a 87% relative risk reduction (RR 0.13; 95% CI 0.04 to 0.41, $p<0.01$) compared to the incidence observed in the placebo + ALN group. A statistically significant risk reduction in the ABL + ALN group compared to the placebo + ALN group was also demonstrated for major osteoporotic fractures (wrist, upper arm, hip, and clinical spine), and clinical fractures. The average gain of BMD in patients treated with ABL + ALN and in those who received placebo + ALN were 12.8% *vs*. 3.5% for lumbar spine, 5.5% *vs*. 1.4% for total hip, and 4.5% *vs*. 0.5% for femoral neck ($p<0.001$ for each site), respectively. There were no differences between groups at the end of the 6-month extension in bone turnover markers and no differences in incidence of adverse effects.

One hundred and five patients from the ACTIVE study (35 treated with ABL 80 μg, 36 with TRPT, and 34 with placebo) undergone a biopsy of the iliac crest between the 12'th and 18'th months (79). The aim of the study was to compare the effects of the three treatments on bone histology and histomorphometry, by assessing changes in mineralisation and microstructure, presence or absence of woven bone, excess osteoid and bone marrow abnormalities. In patients treated with ABL, bone structure, bone matrix, bone cell morphology, and bone marrow were all normal. There was no evidence of excessive osteoid, marrow fibrosis or abnormalities in mineralisation. Moreover, studies of tetracycline labelling showed that all variables related to bone mineralisation and bone formation were similar to those observed in the placebo-treated subjects. There were some significant differences among the three treatment groups in histomorphometric indices. In particular, the mineral apposition rate was higher in the TRPT-treated group than in the placebo-treated group, the eroded surface was lower in the bone of patients treated with ABL than in the placebo-treated group, and cortical porosity was higher in both the ABL and the TRPT treated groups than in the placebo-treated group. It was concluded that there was no evidence of concern for bone safety in patients treated with ABL for 18 months.

Finally, a pre-clinical study assessing the carcinogenic potential of ABL showed comparable incidence of osteosarcoma in rats treated with different daily doses of ABL and human-PTH(1-34) (80), although the increase of incidence of osteosarcoma has never been reported in the clinical experience with TRPT (82).

Romosozumab

Romosozumab (ROMO) is a humanised monoclonal antibody that targets sclerostin. Sclerostin is a glycoprotein

encoded by the SOST gene, produced primarily by osteocytes, that binds to the Frizzled-LRP5-6 complex of the Wnt pathway: this reduces signals of differentiation, maturation, and proliferation of osteoblasts. Moreover, inhibition of Wnt signalling promotes osteoblasts and osteocytes apoptosis, osteoclastogenesis, and OPG expression. There are two genetic diseases characterised by a functional loss of SOST gene and a consequent increased bone formation: Sclerosteosis (83), mutations of the SOST gene that hinder sclerostin synthesis, and van Buchem's disease (84), in which mutations determine deficiency of functional sclerostin. ROMO is the first anti-sclerostin antibody tested in human subjects: by binding to sclerostin, ROMO inhibits the actions of this protein, leading to increased bone formation and reduced bone resorption.

The first clinical study with ROMO was published in 2011 (85). In this study, 72 healthy subjects was treated with a single dose of ROMO subcutaneously (0.1, 0.3, 1, 3, 5, or 10 mg/kg) or intravenously (1 or 5 mg/kg) or with placebo. After 3 months, measurement of BMD showed a significant gain of 5.3% at the lumbar spine and 2.8% at the total hip compared with placebo. The Authors observed a dose-related increases in the bone-formation markers P1NP, bone-specific alkaline phosphatase, and osteocalcin, along with a dose-related decrease in the bone-resorption marker serum CTX, according to the large anabolic window of this drug. In a phase-1b, randomised, double-blind, placebo-controlled study (86) 3-month administration of ROMO determined, compared to placebo, a significant increase in trabecular BMD and cortical thickness calculated with Quantitative Computed Tomography (QCT) and high-resolution QCT and a significant accrual of the bone stiffness evaluated by a finite element analysis.

Furthermore, ROMO, administered at different doses in postmenopausal women with OP, caused a significant increase in vertebral and femoral BMD, compared with ALN and TRPT (87). The Authors reported transitory increases in bone-formation markers and sustained decreases in bone-resorption markers. A subset of this study on 82 patients who received placebo, TRPT or ROMO 210 mg monthly also had lumbar and femoral QTC: after 12 months, ROMO significantly improved integral volumetric BMD and bone mineral content compared to baseline values, and compared to placebo and TRPT. BMD gains were different in trabecular and cortical bone: in particular, trabecular vertebral volumetric BMD increased significantly from baseline with either ROMO (18.3%) and TRPT (20.1%), whereas cortical vertebral volumetric BMD gains were greater with ROMO compared to TRPT (13.7% *vs*. 5.7%, $p<0.0001$). Trabecular hip volumetric BMD gains were significantly greater with ROMO than with TRPT (10.8% *vs*. 4.2%, $p=0.01$), but cortical volumetric BMD gains were comparable (1.1% *vs*. -0.9%, $p=0.12$). Cortical bone mineral content gains were greater with ROMO compared to TRPT at both the spine (23.3% *vs*. 10.9%, $p<0.0001$) and hip (3.4% *vs*. 0.0%, $p=0.03$) (88).

The Fracture Study in Postmenopausal Women with OP (FRAME) (89) was the first multicentre phase 3-trial that studied the efficacy of ROMO in reducing vertebral and non-vertebral fractures. Seven thousand one hundred and eighty postmenopausal women with OP were randomised to receive ROMO 210 mg monthly or placebo for 1 year, after which both groups were switched to denosumab 60 mg every 6 months for a second year. After 12 months, ROMO was associated with a 73% reduction in new vertebral fractures compared to placebo (incidence 0.5% *vs*. 1.8%, $p<0.001$); after 2 years, the cumulative incidence of new vertebral fractures was 75% lower in the ROMO/denosumab group than the placebo/denosumab group (0.6% *vs*. 2.5%, $p<0.001$). Regarding the incidence of non-vertebral fractures, no statistical differences were found between the groups after 12 and 24 months. However, the authors claimed that these data might be due to a bias in the inclusion of a subgroup of patients from Latin America with a lower fracture risk; a post hoc analysis excluding them showed a 42% lower incidence of non-vertebral fractures in the the ROMO/denosumab group than the placebo/denosumab group (90).

Novel evidence on Romosozumab

In a phase-2, double blind, placebo controlled study (91), 252 women with postmenopausal OP were treated with different monthly doses of ROMO (70, 140, or 210 mg) or placebo. After 1 year, compared to placebo, all groups of patients treated with ROMO showed a greater gain of lumbar and femoral BMD. In particular, the largest mean increase from baseline was observed with ROMO 210 mg (lumbar spine=16.9%, total hip=4.7%, and femoral neck=3.8%). Moreover, levels of bone-formation and resorption was evaluated: after 12 months, all doses of ROMO significantly increased the levels of P1NP and reduced the levels of CTX by week 1 ($p<0.001$ *vs*. placebo). Finally, no differences between groups were reported about incidences of adverse events.

The Active-Controlled Fracture Study in Postmenopausal Women with OP at High Risk (ARCH) (92) is a phase 3-multicentre, randomised, double-blind trial which involved 4,093 postmenopausal women with OP and high risk of fracture published in 2017. The patients were treated with monthly sub-cutaneous injection of ROMO 210 mg, or weekly ALN 70 mg; after 12 months, ROMO was withdrawn and both groups of patients continued only with ALN for another year. Over a period of 24 months, cumulative incidence of new vertebral fractures was 6.2% in the ROMO/ALN group, and 11.9% in patients treated with ALN only, with a 48% lower risk of vertebral fractures in the ROMO/ALN group compared to control group ($p<0.001$). Moreover, patients treated with the sequence of ROMO and ALN showed a 27% significant lower risk of clinical fractures (non-vertebral and symptomatic vertebral fractures) compared with the group of patients treated with ALN only. Furthermore, the risk of hip fractures was 38% lower among patients treated with ROMO ($p=0.02$). ROMO caused rapid increase of BMD of lumbar spine, total hip, and femoral neck. ROMO produced a greater effect on BMD than ALN, with

a statistical significant effect observed after 6 months of treatment: the accrual of BMD measured at lumbar spine, total hip, and femoral neck was, respectively, of 11%, 4.3%, and 3.9% in the ROMO/ALN group, and 3.8%, 2.3%, and 1.2% in the group of patients treated with ALN. Moreover, in the first year of observation, ROMO increased levels of P1NP and decreased levels of CTX; after transition to ALN, levels of P1NP and CTX decreased and remained below baseline levels until the end of the study. In patients treated with ALN alone, both P1NP and CTX decreased by the first month of the trial and remained below the baseline levels. This study reported a 1 year-incidence of cardiovascular adverse events that was greater among patients treated with ROMO than in the control group (2.5% *vs*. 1.9%, respectively; odds ratio, 1.31; 95% CI, 0.85 to 2.00); in particular, patients with reported cardiac ischaemic events were 16 in the ROMO/ALN group, and 6 in the ALN (0.8% *vs*. 0.3%). Since constitutive expression of sclerostin was found in the aorta (93), and SOST gene is up-regulated in foci of vascular calcifications (94), it has been hypothesised that sclerostin is a negative regulator of vascular calcification: thus, sclerostin inhibition could promote calcification. However, it is important to note that in the FRAME trial (89) no excess of cardiovascular events was found in the ROMO group. This difference might be explained by differences in the characteristics of the study population (95). In fact, patients from the FRAME trial had a mean age of 70.9 years, and 18.3% of them had one or more vertebral fractures, while patients from ARCH trial had a mean age of 74.3 years and 96.1% of them had at least one vertebral fracture. Patients from the ARCH trial were older and, likely, had more cardiovascular risk factors; furthermore, incidence of cardiovascular adverse events in the control group was two-fold higher in the ARCH trial than in the FRAME trial; finally, this findings might be weakened by the small number of the events and by the lack of statistical power to test the non-inferiority of ROMO *vs*. ALN for safety (96). Furthermore, ALN might have some cardiovascular protection.

In clinical practice, anabolic therapy is often reserved to patients with a high risk of fracture or after failure of therapy with bisphosphonates. As mentioned above, previous studies showed that the use of TRPT in patients who were previously exposed to antiresorptives is associated with lower BMD gain compared with that observed in treatment-naïve patients, particularly at the hip (97, 98). A study assessed BMD changes with ROMO or TRPT for 12 months in 436 postmenopausal women with OP who had been treated with bisphosphonates in the previous 3 years. The results showed that, after 1 year of anabolic therapy, the mean percentage change from baseline of total hip BMD was 2.6% (95% CI 2.2 to 3.0) in the ROMO group and -0.6% (-1.0 to -0.2) in the TRPT group (difference 3.2%, 95% CI 2.7 to 3.8, $p<0.0001$) (99). Secondary end-points included percentage change from baseline in cortical and integral volumetric BMD and integral volumetric Bone Mineral Content (BMC) by QTC, and percentage change from baseline of hip strength (calculated by the finite element analysis) at 6 and 12 months. According to previous studies (100), in patients with high risk of fractures, BMD declined after 6 months of therapy with TRPT. Compared to TRPT group, patients treated with ROMO showed a significantly greater gain in both integral and cortical BMD and BMC at the hip at 6 and 12 months, and trabecular volumetric BMD increased significantly from baseline in both treatment groups (99). Furthermore, patients treated with ROMO showed a greater estimated hip strength respect to TRPT group at 6 and 12 months (2.1% *vs*. -1.0% and 2.5% *vs*. -0.7%, respectively, $p<0.0001$). The reasons for the larger gains in BMD and estimated strength with ROMO are likely related to its mechanism of action, because ROMO has the dual effect of increasing bone formation and decreasing bone resorption, while TRPT is a potent stimulator of both. Similar results were reported by a lumbar and femoral QTC study (101) on a subgroup of the population of a phase-2 trial (87) showed that after 12 months of therapy with ROMO, placebo, or TRPT, patients treated with ROMO presented a significant greater gain of vertebral and femoral strength compared to baseline ($p<0.03$ for all compartments) and also compared to patients treated with TRPT and placebo: the differences on the bone strength increase were 8.9% and 31.2% for lumbar spine (both $p<0.001$), and 4.3% ($p=0.027$) and 3.7 ($p=0.059$) for hip, respectively. Moreover treatment with ROMO was associated with a significant increase of the bone strength evaluated on both the cortical and trabecular compartment of spine and hip compared to baseline and compared to patients treated with TRPT and placebo (101). It is important to note that, in this study TRPT was not associated with a significant gain of femoral strength, as assayed at both cortical and trabecular bone.

Glucocorticoid induced osteoporosis: prevention and treatment in 2017

The American College of Rheumatology released guidelines on assessment and treatment of patients taking glucocorticoids (GCs) (102). The authors divided the patients taking GCs into two groups (women and men ≥40 years and people <40 years). Regarding patients ≥40 years, the risk of fracture was stratified using the World Health Organisation's fracture risk assessment tool (FRAX), a diagnostic instrument used to evaluate the individual 10-year probability of bone fracture risk based on factors as age, weight, height, gender, GCs use, smoking history, alcohol use, fracture history, and rheumatoid arthritis affection (81). According to this tool, patients are considered to have a low, moderate or high risk of fracture if they have FRAX calculated 10 years risk of major fracture of <10%, 10–19%, and ≥20%, respectively. Patients with prior osteoporotic fractures or postmenopausal women with a T-score ≤2.5 measured by DEXA are included in the high risk group. Because FRAX cannot be used for patients <40 years, the authors classified patients with prior osteoporotic fractures as patients with high risk of fracture; patients with a Z-score (measured at hip or spine) <3, a rapid bone loss in 1 year (≥10% at hip or spine), or who are treated with doses of GCs ≥7.5 mg/day for more than 6

months are considered at moderate risk. Patients without other osteoporotic risk factor than GCs treatment are considered at low risk of fracture. All patients have to be assessed for risk of fracture in the first 6 months of GCs therapy. During treatment, the timing of the reassessment of risk factors, incidence of fractures, and therapy efficacy depends by the risk of fracture group and range from 1 year to 3 years.

According the guidelines, all patients need to have adequate calcium intake (1,000–1,200 mg/day), vitamin D intake (600–800 IU/day, with a target serum level >20 ng/ml), and healthy lifestyle factors (a balanced diet, maintaining weight in the recommended range, smoking cessation, regular weight-bearing or resistance training exercise, limiting alcohol intake to 1–2 alcoholic beverages/day).

Patients in treatment with GCs and at moderate-to-high risk of fracture should be treated with oral bisphosphonates. Intra-venous bisphosphonates are indicated in case of comorbidities (such as oesophageal diseases), patient preference, or low of adherence to oral medication regimens. If bisphosphonates are contraindicated, second line treatment is represented by TRPT. If neither oral nor intra-venous bisphosphonates or TRPT treatment is appropriate, denosumab should be used. In postmenopausal women who cannot assume other drugs, raloxifene can be used. It is important to note that because of the lack of evidences about potential foetal harm, women with childbearing potential should be treated with oral bisphosphonates or TRPT only if they are not planning to be pregnant during the OP treatment and are using effective birth control. Finally, for patients with low risk of fractures, no specific pharmacological treatment is recommended.

References

1. KANIS JA: Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: synopsis of a WHO report. *WHO Study Group. Osteoporos Int* 1994; 4: 368-81.
2. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group. *World Health Organ Tech Rep Ser* 1994; 843: 1-129.
3. JOHNELL O, KANIS JA: An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporos Int* 2006; 17: 1726-33.
4. ROSSINI M, ADAMI S, BERTOLDO F *et al*.: Guidelines for the diagnosis, prevention and management of osteoporosis. *Reumatismo* 2016; 68: 1-39.
5. MELTON LJ 3RD, CHRISCHILLES EA, COOPER C, LANE AW, RIGGS BL: Perspective. How many women have osteoporosis? *J Bone Miner Res* 1992; 7: 1005-10.
6. KANIS JA, JOHNELL O, ODEN A *et al*.: Long-term risk of osteoporotic fracture in Malmo. *Osteoporos Int* 2000; 11: 669-74.
7. PISCITELLI P, GIMIGLIANO F, GATTO S *et al*.: Hip fractures in Italy: 2000-2005 extension study. *Osteoporos Int* 2010; 21: 1323-30.
8. LINDSAY R, SILVERMAN SL, COOPER C *et al*.: Risk of new vertebral fracture in the year following a fracture. *JAMA* 2001; 285: 320-3.
9. FINK HA, MILAVETZ DL, PALERMO L *et al*.: What proportion of incident radiographic vertebral deformities is clinically diagnosed and vice versa? *J Bone Miner Res* 2005; 20: 1216-22.
10. BRAUER CA, COCA-PERRAILLON M, CUTLER DM, ROSEN AB: Incidence and mortality of hip fractures in the United States. *JAMA* 2009; 302: 1573-9.
11. SVEDBOM A, HERNLUND F, IVERGARD M *et al*.: Osteoporosis in the European Union: a compendium of country-specific reports. *Arch Osteoporos* 2013; 8: 137.
12. CHEN H, SENDA T, KUBO KY: The osteocyte plays multiple roles in bone remodeling and mineral homeostasis. *Med Mol Morphol* 2015; 48: 61-8.
13. TU X, DELGADO-CALLE J, CONDON KW *et al*.: Osteocytes mediate the anabolic actions of canonical Wnt/beta-catenin signaling in bone. *Proc Natl Acad Sci USA* 2015; 112: E478-86.
14. EMERY JG, MCDONNELL P, BURKE MB *et al*.: Osteoprotegerin is a receptor for the cytotoxic ligand TRAIL. *J Biol Chem* 1998; 273: 14363-7.
15. LI X, ZHANG Y, KANG H *et al*.: Sclerostin binds to LRP5/6 and antagonizes canonical Wnt signaling. *Journal Biol Chem* 2005; 280: 19883-7.
16. DELGADO-CALLE J, SATO AY, BELLIDO T: Role and mechanism of action of sclerostin in bone. *Bone* 2017; 96: 29-37.
17. ARDAWI MS, AL-KADI HA, ROUZI A, QARI MH: Determinants of serum sclerostin in healthy pre- and postmenopausal women. *J Bone Miner Res* 2011; 26: 2812-22.
18. GIUSTINA A, MAZZIOTTI G, CANALIS E: Growth hormone, insulin-like growth factors, and the skeleton. *Endocr Rev* 2008; 29: 535-59.
19. LONGO KA, KENNELL JA, OCHOCINSKA MJ, ROSS SE, WRIGHT WS, MACDOUGALD OA: Wnt signaling protects 3T3-L1 preadipocytes from apoptosis through induction of insulin-like growth factors. *J Biol Chem* 2002; 277: 38239-44.
20. REIJNDERS CM, BRAVENBOER N, TROMP AM, BLANKENSTEIN MA, LIPS P: Effect of mechanical loading on insulin-like growth factor-I gene expression in rat tibia. *J Endocrinol* 2007; 192: 131-40.
21. LEAN JM, JAGGER C J, CHAMBERS TJ, CHOW JW: Increased insulin-like growth factor I mRNA expression in rat osteocytes in response to mechanical stimulation. *Am J Physiol* 1995; 268 (2 Pt 1): p. E318-27.
22. MA X, MENG J, JIA M *et al*.: Exendin-4, a glucagon-like peptide-1 receptor agonist, prevents osteopenia by promoting bone formation and suppressing bone resorption in aged ovariectomized rats. *J Bone Miner Res* 2013; 28: 1641-52.
23. ROCHEFORT GY, PALLU S, BENHAMOU CL: Osteocyte: the unrecognized side of bone tissue. *Osteoporos Int* 2010; 21: 1457-69.
24. TATSUMI S, ISHII K, AMIZUKA N *et al*.: Targeted ablation of osteocytes induces osteoporosis with defective mechanotransduction. *Cell Metab* 2007; 5: 464-75.
25. ROBINSON JA, CHATTERJEE-KISHORE M, YAWORSKY PJ *et al*.: Wnt/beta-catenin signaling is a normal physiological response to mechanical loading in bone. *J Biol Chem* 2006; 281: 31720-8.
26. ROBLING AG, NIZIOLEK PJ, BALDRIDGE LA *et al*.: Mechanical stimulation of bone in vivo reduces osteocyte expression of Sost/sclerostin. *J Biol Chem* 2008; 283: 5866-75.
27. TORRES-LAGARES D, TULASNE JF, POUGET C, LLORENS A, SAFFAR JL, LESCLOUS P: Structure and remodelling of the human parietal bone: an age and gender histomorphometric study. *J Craniomaxillofac Surg* 2010; 38: 325-30.
28. CARTER Y, THOMAS CDL, CLEMENT JG, COOPER DML: Femoral osteocyte lacunar density, volume and morphology in women across the lifespan. *J Struct Biol* 2013; 183: 519-26.
29. VAN STAA TP, LEUFKENS HG, COOPER C: Use of oral corticosteroids in the United Kingdom. *QJM* 2000; 93: 105-11.
30. ANGELI A, GUGLIELMI G, DOVIO A *et al*.: High prevalence of asymptomatic vertebral fractures in post-menopausal women receiving chronic glucocorticoid therapy: a cross-sectional outpatient study. *Bone* 2006; 39: 253-9.
31. VAN STAA TP, LEUFKENS HG, ABENHAIM L, BEGAUD B, ZHANG B, COOPER C: Use of oral corticosteroids and risk of fractures. *J Bone Miner Res* 2000; 15: 993-1000.
32. PEEL NF, MOORE DJ, BARRINGTON NA, BAX DE, EASTELL R: Risk of vertebral fracture and relationship to bone mineral density in steroid treated rheumatoid arthritis. *Ann Rheum Dis* 1995; 54: 801-6.
33. OHNAKA K, TANABE M, KAWATE H, NAWATA H, TAKAYANAGI R: Glucocorticoid suppresses the canonical Wnt signal in cultured human osteoblasts. *Biochem Biophys Res Commun* 2005; 329: 177-81.
34. BUTLER JS, QUEALLY JM, DEVITT BM, MURRAY DW, DORAN PP, O'BYRNE JM: Silencing Dkk1 expression rescues dexamethasone-induced suppression of primary human osteoblast differentiation. *BMC Musculoskelet Dis* 2010; 11: 210.
35. O'BRIEN CA, JIA D, PLOTKIN LI *et al*.: Glucocorticoids act directly on osteoblasts

and osteocytes to induce their apoptosis and reduce bone formation and strength. *Endocrinology* 2004; 145: 1835-41.
36. SHI XM, BLAIR HC, YANG X, MCDONALD JM, CAO X: Tandem repeat of C/EBP binding sites mediates PPARgamma2 gene transcription in glucocorticoid-induced adipocyte differentiation. *J Cell Biochem* 2000; 76: 518-27.
37. ZHANG YY, LI X, QIAN SW *et al*.: Down-regulation of type I Runx2 mediated by dexamethasone is required for 3T3-L1 adipogenesis. *Mol Endocrinol* 2012; 26: 798-808.
38. BRABNIKOVA MARESOVA K, PAVELKA K, STEPAN JJ: Acute effects of glucocorticoids on serum markers of osteoclasts, osteoblasts, and osteocytes. *Calcif Tissue Int* 2013; 92: 354-61.
39. VAN STAA TP, LEUFKENS HG, COOPER C: The epidemiology of corticosteroid-induced osteoporosis: a meta-analysis. *Osteoporos Int* 2002; 13: 777-87.
40. HOFBAUER LC, GORI F, RIGGS BL *et al*.: Stimulation of osteoprotegerin ligand and inhibition of osteoprotegerin production by glucocorticoids in human osteoblastic lineage cells: potential paracrine mechanisms of glucocorticoid-induced osteoporosis. *Endocrinology* 1999; 140: 4382-9.
41. KONDO T, KITAZAWA R, YAMAGUCHI A, KITAZAWA S: Dexamethasone promotes osteoclastogenesis by inhibiting osteoprotegerin through multiple levels. *J Cell Biochem* 2008; 103: 335-45.
42. WHIRLEDGE S, CIDLOWSKI JA: Glucocorticoids, stress, and fertility. *Minerva Endocrinol* 2010; 35: 109-25.
43. SCHAKMAN O, KALISTA S, BARBE C, LOUMAYE A, THISSEN JP: Glucocorticoid-induced skeletal muscle atrophy. *Int J Biochem Cell Biol* 2013; 45: 2163-72.
44. STEWART AF: Hyperparathyroidism, humoral hypercalcemia of malignancy, and the anabolic actions of parathyroid hormone and parathyroid hormone-related protein on the skeleton. *J Bone Miner Res* 2002; 17: 758-62.
45. CORRADO A, SANPAOLO ER, DI BELLO S, CANTATORE FP: Osteoblast as a target of anti-osteoporotic treatment. *Postgrad Med* 2017; 129: 858-65.
46. DRAKE MT, SRINIVASAN B, MODDER UI *et al*.: Effects of parathyroid hormone treatment on circulating sclerostin levels in postmenopausal women. *J Clin Endocrinol Metab* 2010; 95: 5056-62.
47. JOLETTE J, WILKER CE, SMITH SY *et al*.: Defining a noncarcinogenic dose of recombinant human parathyroid hormone 1-84 in a 2-year study in Fischer 344 rats. *Toxicol Pathol* 2006; 34: 929-40.
48. VAHLE JL, LONG GG, SANDUSKY G, WESTMORE M, MA YL, SATO M: Bone neoplasms in F344 rats given teriparatide [rhPTH(1-34)] are dependent on duration of treatment and dose. *Toxicol Pathol* 2004; 32: 426-38.
49. COHEN A, KAMANDA-KOSSEH M, RECKER RR *et al*.: Bone Density After Teriparatide Discontinuation in Premenopausal Idiopathic Osteoporosis. *J Clin Endocrinol Metab* 2015; 100: 4208-14.
50. NEER RM, ARNAUD CD, ZANCHETTA JR *et al*.: Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *New Engl J Med* 2001; 344: 1434-41.
51. ORWOLL ES, SCHEELE WH, 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; 18: 9-17.
52. SAAG KG, ZANCHETTA JR, DEVOGELAER JP *et al*.: Effects of teriparatide versus alendronate for treating glucocorticoid-induced osteoporosis: thirty-six-month results of a randomized, double-blind, controlled trial. *Arthritis Rheum* 2009; 60: 3346-55.
53. MA YL, BRYANT HU, ZENG Q *et al*.: New bone formation with teriparatide [human parathyroid hormone-(1-34)] is not retarded by long-term pretreatment with alendronate, estrogen, or raloxifene in ovariectomized rats. *Endocrinology* 2003; 144: 2008-15.
54. EASTELL R, NICKELSEN T, MARIN F *et al*.: Sequential treatment of severe postmenopausal osteoporosis after teriparatide: final results of the randomized, controlled European Study of Forsteo (EUROFORS). *J Bone Miner Res* 2009; 24: 726-36.
55. YOSHIKI F, NISHIKAWA A, TAKETSUNA M, KAJIMOTO K, ENOMOTO H: Efficacy and safety of teriparatide in bisphosphonate-pretreated and treatment-naive patients with osteoporosis at high risk of fracture: Post hoc analysis of a prospective observational study. *J Orthop Sci* 2017; 22: 330-8.
56. FINKELSTEIN JS, WYLAND JJ, LEE H, NEER RM: Effects of teriparatide, alendronate, or both in women with postmenopausal osteoporosis. *J Clin Endocrinol Metab* 2010; 95: 1838-45.
57. FINKELSTEIN JS, HAYES A, HUNZELMAN JL, WYLAND JJ, LEE H, NEER RM: The effects of parathyroid hormone, alendronate, or both in men with osteoporosis. *New Engl J Med* 2003; 349: 1216-26.
58. COSMAN F, ERIKSEN EF, RECKNOR C *et al*.: Effects of intravenous zoledronic acid plus subcutaneous teriparatide [rhPTH(1-34)] in postmenopausal osteoporosis. *J Bone Miner Res* 2011; 26: 503-11.
59. NAKAMURA Y, SUZUKI T, KAMIMURA M *et al*.: Two-year clinical outcome of denosumab treatment alone and in combination with teriparatide in Japanese treatment-naive postmenopausal osteoporotic women. *Bone Res* 2017; 5: 16055.
60. IDOLAZZI L, ROSSINI M, VIAPIANA O *et al*.: Teriparatide and denosumab combination therapy and skeletal metabolism. *Osteoporos Int* 2016; 27: 3301-7.
61. TSAI JN, UIHLEIN AV, LEE H *et al*.: Teriparatide and denosumab, alone or combined, in women with postmenopausal osteoporosis: the DATA study randomised trial. *Lancet* 2013;. 382: 50-6.
62. LEDER BZ, TSAI JN, UIHLEIN AV *et al*.: Two years of Denosumab and teriparatide administration in postmenopausal women with osteoporosis (The DATA Extension Study): a randomized controlled trial. *J Clin Endocrinol Metab* 2014; 99: 1694-700.
63. TSAI JN, UIHLEIN AV, BURNETT-BOWIE SM *et al*.: Effects of two years of teriparatide, denosumab, or both on bone microarchitecture and strength (DATA-HRpQCT study). *J Clin Endocrinol Metab* 2016; 101: 2023-30.
64. LEDER BZ, TSAI JN, UIHLEIN AV *et al*.: Denosumab and teriparatide transitions in postmenopausal osteoporosis (the DATA-Switch study): extension of a randomised controlled trial. *Lancet* 2015; 386: 1147-55.
65. EBINA K, HASHIMOTO J, KASHII M *et al*.: The effects of switching daily teriparatide to oral bisphosphonates or denosumab in patients with primary osteoporosis. *J Bone Miner Metab* 2017; 35: 91-98.
66. RUSSELL RG, WATTS NB, EBETINO FH, ROGERS MJ: Mechanisms of action of bisphosphonates: similarities and differences and their potential influence on clinical efficacy. *Osteoporos Int* 2008; 19: 733-59.
67. MCCLUNG MR: Inhibition of RANKL as a treatment for osteoporosis: preclenical and early clinical studies. *Curr Osteoporos Rep* 2006; 4: 28-33.
68. LEDER BZ, TSAI JN, JIANG LA, LEE H: Importance of prompt antiresorptive therapy in postmenopausal women discontinuing teriparatide or denosumab: The Denosumab and Teriparatide Follow-up study (DATA-Follow-up). *Bone* 2017; 98: 54-8.
69. KENDLER DL, MARIN F, ZERBINI CAF *et al*.: Effects of teriparatide and risedronate on new fractures in post-menopausal women with severe osteoporosis (VERO): a multicentre, double-blind, double-dummy, randomised controlled trial. *Lancet* 2018; 391: 230-40.
70. IWATA A, KANAYAMA M, OHA F, HASHIMOTO T, IWASAKI N: Effect of teriparatide (rh-PTH 1-34) versus bisphosphonate on the healing of osteoporotic vertebral compression fracture: A retrospective comparative study. *BMC Musculoskelet Disord* 2017; 18: 148.
71. SHIRLEY M: Abaloparatide: First Global Approval. *Drugs* 2017; 77: 1363-8.
72. HATTERSLEY G, DEAN T, CORBIN BA, BAHAR H, GARDELLA TJ: Binding Selectivity of Abaloparatide for PTH-Type-1-Receptor Conformations and Effects on Downstream Signaling. *Endocrinology* 2016; 157: 141-9.
73. LEDER BZ, O'DEA LS, ZANCHETTA JR *et al*.: Effects of abaloparatide, a human parathyroid hormone-related peptide analog, on bone mineral density in postmenopausal women with osteoporosis. *J Clin Endocrinol Metab* 2015; 100: 697-706.
74. MILLER PD, HATTERSLEY G, RIIS BJ *et al*.: Effect of abaloparatide vs placebo on new vertebral fractures in postmenopausal women with osteoporosis: a randomized clinical trial. *JAMA* 2016; 316: 722-33.
75. GENANT HK WU CY, VAN KUIJK C, NEVITT MC: Vertebral fracture assessment using a semiquantitative technique. *J Bone Miner Res* 1993; 8: 1137-48.
76. COSMAN F, HATTERSLEY G, HU MY, WILLIAMS GC, FITZPATRICK LA, BLACK D M: Effects of Abaloparatide-SC on fractures and bone mineral density in subgroups of postmenopausal women with osteoporosis and varying baseline risk factors. *J Bone Miner Res* 2017; 32: 17-23.

77. McCLOSKEY EV, JOHANSSON H, ODEN A *et al*.: The effect of Abaloparatide-SC on fracture risk is independent of baseline FRAX fracture probability: a post hoc analysis of the ACTIVE study. *J Bone Miner Res* 2017; 32: 1625-31.
78. COSMAN F, MILLER PD, WILLIAMS GC *et al*.: Eighteen months of treatment with subcutaneous abaloparatide followed by 6 months of treatment with alendronate in postmenopausal women with osteoporosis: results of the ACTIVExtend trial. *Mayo Clin Proc* 2017; 92: 200-10.
79. MOREIRA CA, FITZPATRICK LA, WANG Y, RECKER RR: Effects of abaloparatide-SC (BA058) on bone histology and histomorphometry: The ACTIVE phase 3 trial. *Bone* 2017; 97: 314-9.
80. JOLETTE J, ATTALLA B, VARELA A *et al*.: Comparing the incidence of bone tumors in rats chronically exposed to the selective PTH type 1 receptor agonist abaloparatide or PTH(1-34). *Regul Toxicol Pharmacol* 2017; 86: 356-65.
81. KANIS JA, JOHNELL O, ODEN A, JOHANSSON H. McCLOSKEY E: FRAX and the assessment of fracture probability in men and women from the UK. *Osteoporos Int* 2008; 19: 385-97.
82. ANDREWS EB, GILSENAN AW, MIDKIFF K *et al*.: The US postmarketing surveillance study of adult osteosarcoma and teriparatide: study design and findings from the first 7 years. *J Bone Miner Res* 2012; 27: 2429-37.
83. BALEMANS W, EBELING M, PATEL N *et al*.: Increased bone density in sclerosteosis is due to the deficiency of a novel secreted protein (SOST). *Hum Mol Genet* 2001; 10: 537-43.
84. BALEMANS W, PATEL N, EBELING M *et al*.: Identification of a 52 kb deletion downstream of the SOST gene in patients with van Buchem disease. *J Med Genet* 2002; 39: 91-7.
85. PADHI D, JANG G, STOUCH B, FANG L, POSVAR E: Single-dose, placebo-controlled, randomized study of AMG 785, a sclerostin monoclonal antibody. *J Bone Miner Res* 2011; 26: 19-26.
86. GRAEFF C, CAMPBELL GM, PENA J *et al*.: Administration of romosozumab improves vertebral trabecular and cortical bone as assessed with quantitative computed tomography and finite element analysis. *Bone* 2015; 81: 364-9.
87. McCLUNG MR, GRAUER A, BOONEN S *et al*.: Romosozumab in postmenopausal women with low bone mineral density. New *Engl J Med* 2014; 370: 412-20.
88. GENANT HK, ENGELKE K, BOLOGNESE MA *et al*.: Effects of romosozumab compared with teriparatide on bone density and mass at the spine and hip in postmenopausal women with low bone mass. *J Bone Miner Res* 2017; 32: 181-7.
89. COSMAN F, CRITTENDEN DB, GRAUER A: Romosozumab Treatment in Postmenopausal Osteoporosis. *New Engl J Med* 2017; 376: 396-7.
90. COSMAN F, CRITTENDEN DB, FERRARI S *et al*.: Romosozumab FRAME Study: a post hoc analysis of the role of regional background fracture risk on nonvertebral fracture outcome. *J Bone Miner Res* 2018; 33: 1407-16.
91. ISHIBASHI H, CRITTENDEN DB, MIYAUCHI A *et al*.: Romosozumab increases bone mineral density in postmenopausal Japanese women with osteoporosis: A phase 2 study. *Bone* 2017; 103: 209-15.
92. SAAG KG, PETERSEN J, BRANDI ML *et al*.: Romosozumab or Alendronate for Fracture Prevention in Women with Osteoporosis. *New Engl J Med* 2017; 377: 1417-27.
93. DIDANGELOS A, YIN X, MANDAL K, BAUMERT M, JAHANGIRI M, MAYR M: Proteomics characterization of extracellular space components in the human aorta. *Mol Cell Proteomics* 2010; 9: 2048-62.
94. ZHU D, MacKENZIE NC, MILLAN JL, FARQUHARSON C, MACRAE VE: The appearance and modulation of osteocyte marker expression during calcification of vascular smooth muscle cells. *PloS One* 2011; 6: e19595.
95. KHOSLA S: Bone diseases: Romosozumab - on track or derailed? *Nature Rev Endocrinol* 2017; 13: 697-8.
96. ROSEN CJ: Romosozumab - Promising or Practice Changing? *New Engl J Med* 2017; 377: 1479-80.
97. BOONEN S, MARIN F, OBERMAYER-PIETSCH B *et al*.: Effects of previous antiresorptive therapy on the bone mineral density response to two years of teriparatide treatment in postmenopausal women with osteoporosis. *J Clin Endocrinol Metab* 2008; 93: 852-60.
98. OBERMAYER-PIETSCH BM, MARIN F, McCLOSKEY EV *et al*.: Effects of two years of daily teriparatide treatment on BMD in postmenopausal women with severe osteoporosis with and without prior antiresorptive treatment. *J Bone Miner Res* 2008; 23: 1591-600.
99. LANGDAHL BL, LIBANATI C, CRITTENDEN DB *et al*.: Romosozumab (sclerostin monoclonal antibody) versus teriparatide in postmenopausal women with osteoporosis transitioning from oral bisphosphonate therapy: a randomised, open-label, phase 3 trial. *Lancet* 2017; 390: 1585-94.
100. MacDONALD HM, NISHIYAMA KK, HANLEY DA, BOYD SK: Changes in trabecular and cortical bone microarchitecture at peripheral sites associated with 18 months of teriparatide therapy in postmenopausal women with osteoporosis. *Osteoporos Int* 2011; 22: 357-62.
101. KEAVENY TM, CRITTENDEN DB, BOLOGNESE MA *et al*.: Greater gains in spine and hip strength for romosozumab compared with teriparatide in postmenopausal women with low bone mass. *J Bone Miner Res* 2017; 32: 1956-62.
102. BUCKLEY L, GUYATT G, FINK HA *et al*.: 2017 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis. *Arthritis Rheumatol* 2017; 69: 1521-37.