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Bone forming agents for the management of osteoporosis

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Osteoporotic fractures are a major cause of morbidity in the population. Antiresorptive agents have been, for more than 15 years, the mainstay of osteoporosis treatment worldwide. However, these medications provide only limited fracture reduction and may be linked to skeletal and non-skeletal long-term safety concerns. Therefore, some patients are considered candidates for bone-forming agents because they remain severely osteoporotic or because they failed antiresorptive therapy. Over the last decade, a particular interest was shown in the development of medications able to increase osteoblasts number, lifespan or activity, hence stimulating bone formation Peptides from the parathyroid hormone family and strontium ranelate were shown to significantly reduce fracture rates. The European Medicines Agency recently confirmed that strontium ranelate is the treatment of choice for patients with severe osteoporosis, men and women, without cardiovascular contra-indications for whom other anti-osteoporosis medications are inappropriate. New therapeutic options, including monoclonal antibodies against sclerostin seem to be promising but their role in the armamentarium of osteoporosis will depend on the results of the current phase 3 studies, assessing anti-fracture efficacy and long-term safety.
KEY WORDS: Bone and bones - Osteoporosis - Strontium ranelate - Teriparatide.

Osteoporosis is defined as a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fractures.[1]

Osteoporotic fractures are a major cause of morbidity in the population.[2]

Approximately 50% of fracture-related deaths in women were due to hip fractures, 28% to clinical vertebral and 22% to other factures.

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Since postmenopausal osteoporosis was originally related to an increase in osteoclastic activity, at the time of menopause, because of the disappearance of the estrogen inhibitory effect on bone resorption, inhibitors of bone resorption were genuinely considered as adequate strategy for prevention and treatment of osteoporosis.

Antiresorptive agents have been, for more than 15 years, the mainstay of osteoporosis treatment worldwide.[2] However, these medications provide only limited fracture reduction [3] and may be linked to skeletal and non-skeletal long-term safety concerns.[4, 5] Therefore, some patients are considered candidates for bone-forming agents because they remain severely osteoporotic or because they failed anti-resorptive therapy.[6] Over the last decade, a particular interest was shown in the development of medications able to increase osteoblasts number, lifespan or activity, hence stimulating bone formation.[2, 7]

Peptides from the parathyroid hormone family

Peptides from the parathyroid hormone (PTH) family have been investigated in the management of osteoporosis for >30 years.[8] A continuous endogenous production or exogenous administration of PTH, as is the case in primary or secondary hyperparathyroidism, can lead to deleterious consequences on the skeleton, particularly on cortical bone. However, intermittent administration of PTH (*e.g.*, through daily subcutaneous injections) results in an

increase of the number and activity of osteoblasts, leading to an increase in bone mass and an improvement in skeletal architecture, at both the trabecular and cortical skeleton. This treatment also increases cortical bone width.

The full length (1-84) PTH molecule and the 1-34 N-terminal fragment (teriparatide) are currently used for the management of osteoporosis. Based on their respective molecular weights, equivalent dose of 1-34 fragment, relative to 1-84 molecule, is 40% (*e.g.*, 20 and 40 μg of 1-34 PTH is equivalent to 50 and 100 μg of 1-84 PTH, respectively).

In order to assess the effects of the 1-34 N-terminal fragment of PTH on fractures, 1637 postmenopausal women with prior spine fractures were randomly assigned to receive 20 or 40 μg of 1-34 PTH or placebo, subcutaneously self-administered daily. Spine radiographs were obtained at baseline and at the end of the study (median duration of observation, 21 months), and serial measurements of bone mass were performed by dual-energy X-ray absorptiometry.

New spine fractures occurred in 14% of the women in the placebo group and in 5% and 4% of the women in the 20- and 40-μg dose groups, respectively. The relative risk of fracture, as compared with the placebo group, was 0.35 and 0.31 (95% CI, 0.22-0.55 and 0.19-0.50), respectively. New non-spine fractures occurred in 6% of the women in the placebo group and 3% of those in each PTH (RR, 0.47 and 0.46, 95% CI, 0.25-0.88 and 0.25-0.86, respectively). PTH had only minor side effects (occasional nausea and headache).[9]

The antifracture efficacy of PTH on spine fracture was not modulated by the age of the subjects (<65 years of age, 65-75 years of age or >75 years of age), prevalent spinal bone mineral density (BMD) values (T-score ≤2.5 or ≥2.5) or number of prevalent fractures (one or two or more fractures).[10]

At the end of this trial, patients were followed for an additional 18-month period without PTH, during which they were allowed to use any anti-osteoporotic medication considered appropriate by their caregiver. Although the proportion of patients having received an inhibitor of bone resorption was slightly higher in patients previously in the placebo group than in the patients having received 20 PTH μg/day, the reduction of spine fractures observed in this particular group during the initial trial was confirmed during this 18-month period (RR, 0.59; 95% CI, 0.42-0.85).[11] At follow-up in 1262 women was conducted up to 30 months after discontinuation of treatment. The hazard ratio for combined teriparatide groups (20 and 40 μg) for the 50-month period after baseline was 0.57 (95% CI; 0.40-0.82), suggesting a sustained effect in reducing the risk of non-spine fragility fracture.[12]

Teriparatide-mediated relative fracture risk reduction was shown to be independent of pretreatment bone turnover, demonstrating that this therapy offers clinical benefit to patients across a range of disease severity.[13]

The European Forsteo Observational Study (EFOS) was designed to examine the effectiveness of teriparatide in postmenopausal women with osteoporosis treated for up to 18 months in normal clinical practice in eight European countries.

All 1648 enrolled women were teriparatide treatment-naive, 91% of them had previously received other anti-osteoporosis drugs, and 72.8% completed the 18-month study. A total of 168 incident clinical fractures were sustained by 138 (8.8%) women (821 fractures/10,000 patient-years). A 47% decrease in the odds of fracture in the last 6-month period compared to the first 6-month period was observed (P<0.005). Mean back pain VAS was reduced by 25.8 mm at end point (P<0.001). The largest improvements were reported in the EUROQUOL-5D, a standardized instrument for use as a measure of health outcomes (EQ-5D), subdomains of usual activities and pain/discomfort. Mean change from baseline in EQ-VAS was 13 mm by 18 months. There were 365 adverse events spontaneously reported, of which 48% were considered related to teriparatide; adverse events were the reason for discontinuation for 79 (5.8%) patients. In conclusion, postmenopausal women with severe osteoporosis who were prescribed teriparatide in standard clinical practice had a significant reduction in the incidence of fragility fractures and a reduction in back pain over an 18-month treatment period. This was associated with a clinically significant improvement in Health-Related Quality of Life (HRQoL).[14] In this study, women aged ≥75 years showed a reduced clinical fracture incidence by 30 months compared with baseline. An improvement in HRQoL and, possibly, an early and significant reduction in back pain were also observed, which lasted for at least 18 months after teriparatide discontinuation when patients were taking other osteoporosis medication. The results should be

interpreted in the context of an uncontrolled observational study.[15, 16]

Finite element (FE) analysis-based strength measures were used to monitor teriparatide therapy and the associated effects on whole bone and local fracture risk. In 44 postmenopausal women with established osteoporosis participating in the European Forsteo Study (EUROFORS), FE models based on high-resolution CT (HRCT) of T(12) were evaluated after 0, 6, 12, and 24 mo of teriparatide treatment (20 µg/d). FE-based strength and stiffness calculations for three different load cases (compression, bending, and combined compression and bending) were compared with volumetric BMD (vBMD) and apparent bone volume fraction (app. BV/TV), as well as DXA-based areal BMD of the lumbar spine. Local damage of the bone tissue was also modeled. Highly significant improvements in all analyzed variables as early as 6 months after starting teriparatide were found. After 24 months, bone strength in compression was increased by 28.1±4.7% (SE), in bending by 28.3±4.9%, whereas app. BV/TV was increased by 54.7±8.8%, vBMD by 19.1±4%, and areal BMD of L(1)-L(4) by 10.2±1.2%. When comparing standardized increases, FE changes were significantly larger than those of densitometry and not significantly different from app. BV/TV. The size of regions at high risk for local failure was significantly reduced under teriparatide treatment. Treatment with teriparatide leads to bone strength increases for different loading conditions of close to 30%.[17]

In an extension of the same EUROFORS, in 758 postmenopausal women with established osteoporosis (N.=181 treatment-naïve) who had at least one postbaseline bone marker determination, teriparatide (20 µg/day) was administered for up to 24 months. Daily teriparatide treatment for 2 year significantly increased spine BMD by 10.7%. At the total hip, BMD increases from baseline at 2 year were 2.5% with teriparatide and the change at the femoral neck was 3.5%.[18] Significant increases in formation markers occurred after 1 month of teriparatide regardless of prior osteoporosis therapy. The absolute increase at 1 month was lower in previously treated *versus* treatment-naïve patients, but after 6 months all groups reached similar levels. N-terminal type I procollagen propeptide (PINP) showed the best signal-to-noise ratio. Baseline PINP correlated positively and significantly with BMD response at 24 months.[19]

High-resolution peripheral quantitative computed tomography (Scanco Medical, Switzerland) (HR-pQCT) was used to perform a standard three-dimensional morphological analysis of the distal radius and tibia in 11 osteoporotic postmenopausal women (mean age, 68.7±12.7 years) at baseline, 6, 12, and 18 months after initiation of 20 µg/day of teriparatide. Ten of the women received bisphosphonate therapy prior to starting on teriparatide. In addition to the standard analysis, cortical BMD, porosity, and thickness using an automated segmentation procedure and estimated bone strength (ultimate stress) using finite element (FE) analysis were quantified.

After 18 months, the authors observed a decrease in total BMD (P=0.03) at the distal radius and a decrease in cortical BMD at the distal radius (P=0.05) and tibia (P=0.01). The declines in cortical BMD were associated with trends for increased cortical porosity at both sites. At the distal radius, 18 months of teriparatide treatment was also associated with trabecular thinning (P=0.009) and reduced trabecular bone volume ratio (P=0.08). Despite these changes in bone quality, bone strength was maintained over the 18-month follow-up.[20]

To compare the bone anabolic drug teriparatide (20 µg/day) with the antiresorptive drug alendronate (10 mg/day) (ALN) for treating glucocorticoid-induced osteoporosis (OP), a 36-month, randomized, double-blind, controlled trial was conducted in 428 subjects with OP (ages 22-89 years) who had received ≥5 mg/day of prednisone equivalent for ≥3 months preceding screening. Measures included changes in lumbar spine and hip BMD, changes in bone biomarkers, fracture incidence, and safety.

Increases in BMD from baseline were significantly greater in the teriparatide group than in the ALN group, and at 36 months were 11% *versus* 5.3% for lumbar spine, 5.2% *versus* 2.7% for total hip, and 6.3% *versus* 3.4% for femoral neck (P<0.001 for all). In the teriparatide group, median percent increases from baseline in PINP and osteocalcin (OC) levels were significant from 1 to 36 months (P<0.01), and increases in levels of C-terminal telopeptide of type I collagen (CTX) were significant from 1 to 6 months (P<0.01). In the ALN group, median percent decreases in PINP, OC, and CTX were significant by 6 months and remained below baseline through 36 months (P<0.001). Fewer subjects had vertebral fractures in the teriparatide group than in the ALN group (3 [1.7%] of 173 *versus* 13 [7.7%] of 169; P=0.007), with most occurring during the first 18

months. There was no significant difference between groups in the incidence of nonvertebral fractures (16 [7.5%] of 214 subjects taking teriparatide *versus* 15 [7%] of 214 subjects taking ALN; P=0.843). More subjects in the teriparatide group (21%) *versus* the ALN group (7%) had elevated predose serum calcium concentrations (P<0.001).[21]

Full-length recombinant human PTH (1-84) has also been investigated in the management of postmenopausal osteoporosis. It has been postulated that the C-terminal region of PTH, which teriparatide lacks, also has biological functions in the bone that are mediated by a novel receptor, specific for this region of the hormone. Teriparatide, for instance, has been associated with osteosarcoma in rats, treated with massive doses during most of their lifespan, possibly related to its anti-apoptotic effects in bone cells and decrease in production of C-terminal PTH fragments. In contrast, researchers suggest that PTH (1-84) is likely to not have such effect due to the pro-apoptotic effects of C-terminal PTH fragments that maintain normal bone cell turnover.[22, 23]

In a Phase II study, women self-administered PTH (50, 75 or 100 μg) or placebo by daily subcutaneous injection for 12 months. The 100-μg dose increased BMD significantly at 3 months and 12 months (+7.8%). Bone area also significantly increased (+2%). Non significant decrease (-0.9%) in total hip BMD occurred during the first six months with the 100 μg dose, but this trend reversed (+1.6%) during the second six months. Bone turnover markers increased during the first half of the study and were maintained at elevated levels during the second six months. Dose-related incidences of transient hypercalcemia occurred but only 1 patient (100-μg group) was withdrawn because of repeated hypercalcemia.[23, 24]

Evidence from the treatment of osteoporosis with parathyroid hormone (TOP) study, including women with low BMD (with or without previous fracture) suggest that PTH (1-84) reduced the incidence of vertebral fractures in all patients and prevented the incidence of first vertebral fracture in women with postmenopausal osteoporosis.[23] Reduction of nonvertebral or hip fractures does not clearly appear from the currently available data.[24, 25]

HR-pQCT was used to detail effects on compartmental geometry, density and microarchicture as well as FE estimated integral strength at the distal radius and tibia in postmenopausal osteoporotic women treated with PTH 1-34 (20 μg sc. daily, N.=18) or PTH 1-84 (100 μg sc. daily, N.=20) for 18 month in an open label, non-randomized study. A group of postmenopausal osteoporotic women receiving zoledronic acid (5 mg infusion once yearly, N.=33) was also included. Anabolic therapy increased cortical porosity in radius (PTH 1-34 32±37%, PTH 1-84 39±32%, both P<0.001) and tibia (PTH 1-34 13±27%, PTH 1-84 15±22%, both P<0.001) with corresponding declines in cortical density. With PTH 1-34 increases in cortical thickness in radius (2±3.8%, P<0.05) and tibia (3.8±10.4%, P<0.01) were seen. Trabecular number increased in tibia with both PTH 1-34 (4.2±7.1%, P<0.05) and PTH 1-84 (5.3±8.3%, P<0.01). Zoledronic acid did not impact cortical porosity at either site, but increased cortical thickness (3±3.5%, P<0.01), total (2.7±2.5%, P<0.001) and cortical density (1.5±2%, P<0.01) in tibia as well as trabecular volume fraction in radius (2.5±5.1%, P<0.05) and tibia (2.2±2.2%, P<0.01). FE estimated bone strength was preserved, but not increased, with PTH 1-34 and zoledronic acid at both sites, while it decreased with PTH 1-84 in radius (-2.8±5.8%, P<0.05) and tibia (-3.9±4.8%, P<0.001). Conclusively, divergent treatment-specific effects in cortical and trabecular bone were observed with anabolic and zoledronic acid therapy.[26]

A Markov economic model of osteoporosis in postmenopausal women was developed using 6-month cycles and a lifetime horizon. The model was populated with patients similar to the Swedish cohort of the EUROFORS (postmenopausal women; mean age: 70 years, total hip T-score: -2.7 and 3.3 previous fractures). The cost effectiveness of both teriparatide and PTH (1-84) was estimated compared to no treatment and each other. Relative effectiveness assumptions were based on efficacy estimates from two phase III clinical trials. The cost per quality-adjusted life years (QALY) gained for teriparatide *vs*. no treatment was estimated at € 43,473 and PTH (1-84) was estimated at € 104,396. Teriparatide was indicated to be less costly and associated with more life-years and QALYs than PTH (1-84). When assuming no treatment effect on hip fractures the cost per QALY gained was € 88,379. In the sensitivity analysis the cost effectiveness did not alter substantially with changes in the majority of the model parameters except for the residual effect of the treatment after stopping therapy.[27]

Once-weekly subcutaneous injections of teri-

paratide (56.5 μg) to Japanese osteoporotic women reduced the risk of new vertebral fracture with a cumulative incidence of 3.1% in the teriparatide group, compared with 14.5% in the placebo group (P<0.01), and a relative risk of 0.20 (95% confidence interval, 0.09 to 0.45). At 72 weeks, teriparatide administration increased BMD by 6.4%, 3%, and 2.3% at the lumbar spine, the total hip, and the femoral neck, respectively, compared with the placebo (P<0.01). Adverse events (AE) and the drop-out rates by AE were more frequently experienced in the teriparatide group, but AE were generally mild and tolerable.[28]

Significant fracture risk reductions were observed in the subgroups of individuals aged <75 years (relative risk [RR] 0.06, P=0.007) and ≥75 years (RR 0.32, P=0.015). A significant risk reduction was observed among patients with prevalent vertebral fracture in the subgroup with 1 (RR 0.08, P=0.015) or ≥2 (RR 0.29, P=0.009) prevalent vertebral fractures, and in those with grade 3 deformity (RR 0.26, P=0.003). Significant risk reduction was observed in the subgroup with lumbar BMD ≤2.5 SD (RR 0.25, P=0.035). In the teriparatide group, no incident fracture was observed in the subgroups with a prevalent vertebral fracture number of O, with grade 0-2 vertebral deformity, or with lumbar BMD ≥2.5 SD.[29]

A randomized, double-blind trial to assess the effect of 28.2 μg weekly teriparatide *versus* placebo (1.4 μg teriparatide) on reduction of the incidence of vertebral fractures included patients with primary osteoporosis with one to five vertebral fractures and capable of self-supported walking. Attention was focused on incident vertebral fractures, change in BMD of the lumbar spine, and safety. A total of 316 subjects participated in the study, which lasted up to 131 weeks. Incident vertebral fractures occurred in 3.3% of subjects in the 28.2 μg teriparatide-treated group and 12.6% of subjects in the placebo group during the 78-weeks study period. Kaplan-Meier estimates of risk after 78 weeks were 7.5 and 22.2% in the teriparatide and placebo groups, respectively, with a relative risk reduction of 66.4% by teriparatide (P=0.008). Lumbar BMD in the 28.2 μg teriparatide group increased significantly by 4.4±4.7% at 78 weeks, which was significantly higher than the corresponding data in the placebo group (P=0.001). Adverse events were observed in 86.7% of individuals in the teriparatide group and 86.1% of those in the placebo group.[30]

In a 6-month, randomized, placebo-controlled, positive control, multidose daily administration studies, 165 postmenopausal women (mean age, 64 yr) with osteoporosis received a teriparatide patch with a 20-, 30-, or 40 μg dose or a placebo patch, self-administered daily for 30-min wear time, or 20 μg of TPTD injected daily. Teriparatide delivered by transdermal patch significantly increased lumbar spine BMD vs. placebo patch in a dose-dependent manner at 6 months (P<0.001). Teriparatide 40-μg patch increased total hip BMD compared to both placebo patch and teriparatide injection (P<0.05). Bone turnover markers (PINP and CTX) increased from baseline in a dose-dependent manner in all treatment groups and were all significantly different from placebo patch (P<0.001). All treatments were well tolerated, and no prolonged hypercalcemia was observed.[31]

An enteric-coated oral tablet formulation of rhPTH(1-31)NH(2) resulted in similar pharmacokinetic profiles at baseline dose and after 24 weeks with mean C(max) values similar to subcutaneous administration. In the rhPTH(1-31)NH(2) arm, a 2.2% increase in lumbar spine BMD was observed compared to baseline (P<0.001), while no change was observed in the placebo arm. Open-label teriparatide, resulted in a 5.1% increase in LS BMD (P<0.001). In the oral PTH study arm, the bone formation marker OC was increased by 32%, 21% and 23% at Weeks 4, 12 and 24, respectively. There was no significant increase in the level of the bone resorption marker CTX.[32]

It is important to know whether PTH will yield skeletal benefits in patients who have been previously exposed to long term use of inhibitors of bone resorption.

In a small cohort of women previously treated with hormone replacement therapy (HRT), and continuing their hormonal treatment, PTH (1-34 25 μg daily) given for 3 years, induced significant increases in vertebral (13%), hip (2.7%) and total body (8%) (N.=17) BMD, while no changes were observed in women continuing their HRT alone (N.=17). When vertebral fractures were defined as a 15% reduction in vertebral height, a significantly lower number of women experienced a new vertebral fracture in PTH plus HRT group (N.=2) compared to HRT alone (N.=7). This difference, however, was no longer significant when the threshold for fracture definition was set up at a 20% decrease in vertebral height.[33] Similar results were observed in women with oste-

oporosis who had been on HRT for at least 2 years. In this study, the respective increases in BMD observed, in the PTH plus HRT group after 3 years, were 13.4%, 4.4% and 3.7% for the spine, total hip and total body respectively. BMD measurements remained stable 1 year after discontinuation of PTH. In the PTH plus HRT group, biochemical markers of bone formation, bone specific alkaline phosphatase, (BSAP) and resorption urinary N-terminal telopeptide of type I collagen (NTX) peaked at 6 months and subsequently remained elevated until 30 months, at which their levels were indistinguishable from baseline. PTH plus HRT reduced the percent of women who had vertebral fractures from 37.5% to 8.5% (using a 15% height reduction criterion) and from 25% to 0% (using a 20% height reduction criterion) compared with women receiving HRT alone.[34]

In corticosteroid-induced osteoporosis (GIOP), a similar daily dose of 1-34 PTH (25 μg) was given for 12 months to women 50-82 years of age, who had been taking HRT for at least 1 year. The difference in mean changes in BMD of the lumbar spine between the PTH plus HRT and the HRT only groups, after 1 year, was 33.5% when assessed by quantitative computed tomography (QCT) and 9.8% when assessed by DXA. The changes in the hip and the forearm were not significantly different between the groups. During the first 3 months of PTH treatment, markers of bone formation (OC, BSAP) increased to nearly 150% whereas markers of bone resorption, urinary deoxypyridinoline (DPD) increased only 100%.[35] The same group published a 12-month follow up of this study, after PTH was discontinued. Biochemical markers of bone turnover returned to baseline values, within 6 months of discontinuing the PTH treatment. After 12 months of treatment (PTH plus HRT) and 12 months of follow-up (HRT only), an additional increase in spinal BMD was observed, compared to the end of treatment and a significant increase in hip BMD was observed, which was not present after 12 months. The authors speculate that the additional increase in BMD that occurred after the discontinuation of PTH is most likely a result of filling in of the remodelling space that was excavated in response to PTH treatment.[36]

More recently, the effect of PTH (1-34, 20 μg/day) therapy on BMD and bone turnover were assessed in women with osteoporosis who were previously treated with either ALN or raloxifene (RLX) therapy for 18-36 months.[37] Median baseline bone turnover marker levels in prior ALN patients were about one-half those of prior RLX patients. After 1 month of PTH treatment, both prior RLX and prior ALN groups showed statistically significant increases in serum OC, P1NP and BSAP. There was a consistent trend among all bone turnover markers in prior RLX patients to show greater early increases and to remain about one-third higher during the entire 18-month treatment period than prior ALN patients. However, the only statistically significant differences between prior treatment groups were at the 1-month observation for BSAP, OC and P1NP. During the first 6 months, there were statistically significant group differences in BMD changes at the hip (prior ALN -1.8% *vs*. prior RLX +0.5%) and at the spine (prior ALN +0.5% *vs*. prior RLX +5.2%). The positive slopes in hip and lumbar spine BMD were similar in both groups between 6 and 18 months. After 18 months, mean lumbar spine BMD increases were significantly greater in prior RLX (10.2%) compared to prior ALN (4.1%) and a significant increase in total hip BMD was observed in prior RLX (1.8%) but not in prior ALN. The authors concluded that teriparatide treatment stimulates bone turnover in patients pretreated with both ALN and RLX and that, with the exception of the 1-month values, the increase in bone markers were comparable with those observed in treatment-naïve patients. While prior ALN treatment seems to inhibit the early increase in spinal BMD and its associated with an early decrease in a hip BMD, this trend is reversed after the first 6 months of treatment. From this time on, prior RLX and prior ALN patients exhibit a similar behavior in terms of BMD increases.[38]

In conclusion, patients pretreated with inhibitors of bone resorption, who have not achieved a full therapeutic response, are good candidates for treatment with anabolic agents. The increase in bone turnover that follows the introduction of 1-34 PTH in patients treated with an antiresorptive agent is similar to that observed in treatment-naïve patients and the pattern of BMD increase is also identical, with the exception of a 6-month delay in the spinal and hip BMD changes observed in prior ALN treated subjects.

Another issue is whether the use of an antiresorptive agent and an anabolic drug such as PTH together, would provide a therapeutic advantage by combining different mechanisms for the reduction of the risk of fractures. While previously mentioned trials reported the addition of PTH to ongoing ERT/

HRT,[28-32] fewer data are available for the use of antiresorptive agents together with PTH, from the start of therapy in previously untreated patients.

The Parathyroid Hormone and Alendronate Study (PATH) addressed this question by following, for 12 months, 238 PMW (who were not using BP), with low BMD at the hip or spine. They were randomly assigned to daily treatment with PTH (1-84, 100 μg/day) ALN (10 mg/day) or both. The areal BMD at the spine (DXA) increased in all the treatment groups, and there was no significant difference in the increase between the PTH and the PTH-ALN group. The volumetric density (QCT) of the trabecular bone at the spine increased substantially in all groups, but the increase in the PTH alone group was about twice that found in either of the other groups. Bone formation (P1NP) increased markedly in the PTH group but not in the combination therapy group. Bone resorption (CTX) decreased in the combination therapy group and the ALN group. The authors concluded of no evidence of synergy between PTH and ALN. They considered that the changes in the volumetric density of trabecular bone, the cortical volume at the hip (significantly increased in the PTH group but not in the other treatment groups) and the levels of bone markers suggest that the concurrent use of ALN may reduce the anabolic effects of PTH.[37]

These results were in close concordance with those observed in men treated with ALN (10mg/day given for 30 months), PTH (1-34, 40 μg/day begun at month 6) or both. BMD of the lumbar spine and femoral neck (DXA) increased significantly more in men treated with PTH alone than in those in the other groups. At 12 months, changes in BSAP were significantly greater in the PTH group than in the ALN or PTH plus ALN groups. The authors concluded that ALN impairs the ability of PTH to increase BMD at the lumbar spine and the femoral neck in men, through an attenuation of PTH-induced stimulation of bone formation by ALN.[39] These results suggest that if therapy with PTH is contemplated, it should be used alone and not with ALN.[40]

To evaluate the effects of combination therapy including an intravenous infusion of zoledronic acid (ZOL) 5 mg and daily subcutaneous teriparatide 20 μg *versus* either agent alone on bone mineral density (BMD) and bone turnover markers, a 1-year multicenter, multinational, randomized, partial double-blinded, controlled trial was designed. 412 postmenopausal women with osteoporosis (mean age 65±9 years) were randomized to a single infusion of ZOL 5 mg plus daily subcutaneous teriparatide 20 μg (N.=137), ZOL alone (N.=137), or teriparatide alone (N.=138). The primary endpoint was percentage increase in lumbar spine BMD (assessed by DXA) at 52 weeks *versus* baseline. Secondary endpoints included change in BMD at the spine at earlier time points and at the total hip, trochanter, and femoral neck at all time points. At week 52, lumbar spine BMD had increased 7.5%, 7%, and 4.4% in the combination, teriparatide, and ZOL groups, respectively ($P<0.001$ for combination and teriparatide *versus* ZOL). In the combination group, spine BMD increased more rapidly than with either agent alone ($P<0.001$ *versus* both teriparatide and ZOL at 13 and 26 weeks). Combination therapy increased total-hip BMD more than teriparatide alone at all times (all $P<0.01$) and more than ZOL at 13 weeks ($P<0.05$), with final 52-week increments of 2.3%, 1.1%, and 2.2% in the combination, teriparatide, and ZOL groups, respectively.

The authors concluded that while teriparatide increases spine BMD more than ZOL and ZOL increases hip BMD more than teriparatide, combination therapy provides the largest, most rapid increments when both spine and hip sites are considered.[41]

In a randomized, double-blinded study of risedronate (RIS) (35 mg weekly plus placebo injection), teriparatide (20 μg subcutaneously daily plus placebo tablet), or both RIS plus teriparatide (combination) for 18 months in 29 men with low BMD, the primary endpoint was percentage change in lumbar spine (LS) BMD at 18 months. Secondary outcomes included changes in bone markers and BMD at other sites and interim time-points. All therapies increased LS BMD as compared with baseline ($P<0.05$), but there were no between-group differences at 18 months. Total hip (TH) BMD increased to a greater extent in the combination group (mean±SEM, 3.86±1.1%) *versus* teriparatide (0.29±0.95%) or RIS (0.82±0.95%; $P<0.05$ for both). Femoral neck (FN) BMD also increased more in the combination group (8.45±1.8%) *versus* RIS (0.50±1.7%; $P=0.002$), but was not different from teriparatide alone. In the combination group, P1NP and CTX increased rapidly, mirroring the teriparatide-alone arm. There were no between-group differences in adverse events. Combination teriparatide and RIS increased BMD at the LS, TH as well as the FN and provided greater BMD increases at the TH than monotherapy.[41]

A recent trial compared combined teriparatide and denosumab with both agents alone. This study enrolled postmenopausal women with osteoporosis. Patients were assigned in a 1:1:1 ratio to receive 20 μg teriparatide daily, 60 mg denosumab every 6 months, or both. BMD was measured at 0, 3, 6 and 12 months; 94 (94%) of 100 eligible women completed at least one study visit after baseline. At 12 months, posterior-anterior lumbar spine BMD increased more in the combination group (9.1%, [SD 3.9] than in the teriparatide (6.2% [4.6], P=0.0139) or denosumab (5,35% [3.3], P=0.0005) groups. Femoral-neck BMD also increased more in the combination group (4.2% [3] than in the teriparatide (0.8% [4.1], P=0.0007) and denosumab (2.1% [3.8], P=0.0238) groups, as did total-hip BMD (combination, 4.9% [2.9]; teriparatide, 0.7% [2.7], P<0.0001; denosumab 2.5% [2.6], P=0.0011).

The conclusion was that combined teriparatide and denosumab increased BMD more than either agent alone and more than has been reported with approved therapies. The authors suggested that combination treatment might, therefore, be useful to treat patients at high risk of fracture.[42-44]

Whether this can be extrapolated to other BP or other anti-resorptive agents remains unclear and will only be concluded after the appropriate study (ideally including fracture end-points) will be performed.

The disappointment generated by the apparent absence of synergistic effect of PTH and ALN should not hide the potential benefit of using an inhibitor of resorption after treatment with PTH. Few studies have specifically addressed this issue, so far, but data strongly suggest that the administration of ALN for 1 year after 1 year of treatment with PTH maintains or even potentiates the skeletal benefit observed during PTH treatment.[34] Such results are also supported by recent findings from the previously described EUROFORS, which compared BMD effects and clinical safety of three follow-up treatments (anabolic with teriparatide, antiresorptive with RLX, or no active treatment) after 1 year of teriparatide. Postmenopausal women with osteoporosis and a recent fragility fracture received open-label teriparatide (20 μg/d) for 12 months before they were randomized (3:1:1) to continue teriparatide (N.=305), switch to RLX 60 mg/d (N.=100), or receive no active treatment for the second year (N.=102). All patients received calcium and vitamin D supplementation. Daily teriparatide treatment for 2 year significantly increased spine BMD by 10.7%. Patients receiving RLX in year 2 had no further change in spine BMD from year 1 (change from baseline, 7.9%), whereas patients receiving no active treatment had a BMD decrease of 2.5% in year 2 (change from baseline, +3.8%). At the total hip, BMD increases from baseline at 2 year were 2.5% with teriparatide, 2.3% with RLX, and 0.5% with no active treatment; the respective changes at the femoral neck were 3.5%, 3.1% and 1.3%. However, the study had insufficient power to assess antifracture efficacy.[2, 18]

Two recent reports suggested that teriparatide might be an interesting addition to the armementarium of atypical femoral fractures associated with long-term use of bisphosphonate therapy, in postmenopausal osteoporotic women, by improving healing of atypical fractures and restoration of bone quality.[42, 43]

Two reports from Asia,[44, 45] which were not supported by a European case report [46] suggested that short-term teriparatide therapy might also be an adjunctive modality for the management of bisphosphonate-related osteonecrosis of the jaw.

Strontium ranelate

Strontium ranelate (SR) is composed of an organic moiety (ranelic acid) and of two atoms of stable (non-radioactive) strontium. Its chemical name is: 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-3-thiophenacetic acid distrontium salt. The strontium content in SR is 34.1%,[47] the relative molecular weight (anhydrous) is 513.49.

It is thought to be the first anti-osteoporotic agent that appears to simultaneously increase bone formation and decrease bone resorption, thus resulting in the creation of new bone.[48] Specifically, the dual mode of action of SR is due to direct effects on both osteoblasts and osteoclasts, as reflected by the changes in bone markers in clinical trials.[49, 50]

Results obtained from studies using transiliac bone biopsies as primary outcomes are difficult to reconciliate. There is, however, a general consensus to consider that bone quality determinants at tissue level are preserved in postmenopausal osteoporotic women treated for several years with SR.[51] Similarly, after 3 years of treatment, the mean rate of substitution of calcium by strontium in bone remains low (4.5%) and crystal or unit cells characteristics were not influenced by the presence of SR.[52]

In a recent multicenter, international, double-blind, controlled study, conducted in 387 postmenopausal women with osteoporosis, transiliac bone biopsies were performed at baseline and after 6 or 12 months of treatment with either SR 2 g per day (N.=256) or ALN 70 mg per week (N.=131). No deleterious effect on mineralization of SR or ALN was observed. In the intention-to-treat (ITT) population (268 patients with paired biopsy specimens), most static parameters of formation were maintained between baseline and the last value with SR but significant decreases in the dynamic parameters of formation were noted at M6 and M12 in SR. Compared with ALN, the bone formation parameters at M6 and M12 were always significantly higher (P>0.001) with SR. Compared to the baseline paired biopsy specimens, none of the changes observed in the cancellous bone structure parameters at M12 with SR was significantly different from ALN. In conclusion, this large controlled paired-biopsy study over one year shows that the bone formation remains higher with a lower diminution of the bone remodeling with SR *versus* ALN. However, from these results SR did not show a significant anabolic action on bone remodeling.[53]

These results are surprisingly in conflict with previous work from the same group which assessed 141 transiliac bone biopsies, obtained from 133 postmenopausal osteoporotic women: 49 biopsies after 1-5 year of 2 g/d SR and 92 biopsies at baseline or after 1-5 year of placebo.

They conclude that bidimensional histomorphometry provided a demonstration of the bone safety of SR, with significantly higher mineral apposition rate (MAR) in cancellous bone (+9%) *versus* control, P=0.019) and borderline higher in cortical bone (+10%, P=0.056). Osteoblast surfaces were significantly higher (+38% *versus* control, P=0.047). Tridimensional analysis of 3-year biopsies with treatment (20 biopsies) and placebo (21 biopsies) using microCT showed significant changes in microarchitecture with, in the SR group, higher cortical thickness (+18%, P=0.008) and trabecular number (+14%, P=0.05), and lower structure model index (-22%, P=0.01) and trabecular separation (-16%, P=0.04), with no change in cortical porosity.[54]

These results have also to be balanced by another trial, comparing bone biopsies obtained in patients treated for 6 months either with teriparatide (20 µg/d) or with SR (2 g/d). Whereas most of the bone formation and mineralization variables were numerically higher for teriparatide, few of the differences reached statistical significance, *e.g.*, the formation rate per bone surface did not.[55]

Another study on a series of five consecutively taken bone biopsies from an osteoporotic individual over a six-year period analyzed changes in cellular characteristics, bone microstructure and mineralization caused by a therapy switch from an antiresorptive (bisphosphonate) to a dual action bone agent (SR).

Four biopsies were taken during biophosphonate therapy and one biopsy was taken after one year of SR treatment.

Microstructural data revealed a notable increase in bone volume fraction after one year of SR treatment compared to the bisphosphonate treatment period. Indices of connectivity density, structure model index and trabecular bone pattern factor were predominantly enhanced indicating that the architectural transformation from trabecular rods to plates was responsible for the bone volume increase and less due to changes in trabecular thickness and number. Administration of SR following bisphosphonates led to a maintained mineralization profile with an uptake of strontium on the bone surface level.[56]

Eventually, paired iliac crest biopsies from 15 patients post-BP therapy were subjected to a baseline biopsy and a follow-up biopsy after treatment with 2 g SR day^{-1} after either 6 months (N.=5) or 12 months (N.=10). Dual energy X-ray absorptiometry scans, serum parameters and biochemical markers were obtained. Quantitative backscattered electron imaging and energy-dispersive X-ray analyses combined with micro-A-ray fluorescence determinations were performed to observe any mineralization changes. After 6 months of SR treatment, increases in osteoid surface and strontium content were observed, but no other indices showed significant change. After 12 months of SR treatment, there was a significant increase in bone volume and trabecular thickness, and further increases in strontium content and backscattered signal intensity. These structural changes were accompanied by increased numbers of osteoblasts and increased osteoid surface and volume. Additionally, low bone resorption, as measured by a low number of osteoclasts were observed. SR treatment led to increase osteoid indices and bone volume, which is indicative of newly formed bone, while osteoclasts were still suppressed.[57]

SR has been investigated in a large phase 3 pro-

gram, initiated in 1996, which includes two clinical trials for the treatment of established osteoporosis.[46, 58, 59] The SOTI study was aimed at assessing the effect of SR on the risk of vertebral fractures.[46] The TROPOS trial aimed to evaluate the effect of SR on peripheral (non-spinal) fractures.

In SOTI, a total of 1649 postmenopausal osteoporotic women were randomized to SR or placebo for 4 years, followed by a 1-year treatment-switch period for half of the patients (mean age 70 years), whereas 5091 patients were included in TROPOS (mean age 77 years) for 5 years. In these two studies, the main statistical analysis was performed, after 3 years, in the intent-to-treat population (ITT), defined as patients who took at least one sachet of study treatment and with baseline and postbaseline evaluation of the main criteria.

The primary analysis of SOTI [30] (ITT, N.=1442), evaluating the effect of SR 2 g/day on vertebral fracture rates, revealed a 41% reduction in RR of experiencing a new vertebral fracture (semiquantitative assessment) with SR throughout the 3-year study compared with placebo (139 patients with vertebral fracture *versus* 222, respectively [RR 0.59; 95% CI 0.48-0.73; P<0.001]). The risk of clinical vertebral fractures, which are defined as associated with height loss or back pain and therefore considered as the most severe, was reduced by 38% (RR 0.62; 95% CI 0.47-0.83; P<0.001). The RR of experiencing a new vertebral fracture was significantly reduced in the SR group as compared with the placebo group for the first year. Over the first 12 months, RR reduction was 49% (RR 0.51; 95% CI 0.36-0.74; Cox model P<0.001). In SOTI, the lumbar BMD increased by 14.4% in the treated group in comparison with the placebo group (P<0.001). At the third month of therapy, the serum concentration of bone-specific alkaline phosphatase was higher in the SR group than in the placebo group (a treatment-related increase of 8.1%, P<0.001), and this difference persisted at each evaluation during the 3 years. The concentration of CTX was lower in the SR group than in the placebo group at month 3 (a treatment-related difference of 12.2%, P<0.001) and at each subsequent evaluation during the 3 years (P<0.001).[33] C-terminal propeptide of type I procollagen (PICP) and N-telopeptide cross-links (U-NTX) confirmed the dual mode of action of SR. PICP was significantly increased at all time points, compared to the placebo group, while U-NTX was significantly decreased in the SR group over the 3 years of follow-up.[60] SR was well tolerated without any specific adverse events.[49, 59, 61]

The risk of new vertebral fracture over the 4-year treatment period was reduced by 33% with SR, relative to placebo (RR 0.67; 95% CI 0.55-0.81; P<0.001). Similarly, the risk of new clinical vertebral fractures was reduced by 36% (RR 0.64; 95% CI 0.49-0.83; P<0.01) over 4 years. The number of patients needed to treat for 4 years to prevent one new vertebral fracture was 11 (95% CI 7-24). Among severely affected patients (with two or more prevalent vertebral fractures at baseline), risk reduction with SR was 36% (RR, 0.64; 95% CI 0.50-0.81; P<0.001). The total number of new vertebral fractures was significantly lower in the SR group (275) than in the placebo group (421; P<0.001). The risk of new clinical vertebral fracture was reduced by 36% with SR relative to placebo (RR 0.64; 95% CI 0.49-0.83; P<0.001).

In the patients maintained on SR, the progressive increase in lumbar spine seen throughout the 4 years of the trial continued during the fifth year, with an increase of 1.2±5.8% between month 48 and the end of treatment. In the patients switched to placebo, the increase in BMD began to reverse after the switch (-3.2±5.8%) between month 48 and the end of treatment, although BMD was still substantially higher at month 60 (0.819±0.147 g/cm²) compared with month 0 (0.734±0.123 g/cm²). Both the increase in lumbar BMD in the group maintained on SR and the decrease in the group switched to placebo between month 48 and the end of treatment were significant (P<0.001 and P=0.002, respectively). BMD in the group switched to placebo increased after subsequent switch back to SR; the increase between month 48 and the end of treatment (5.3±7.3%) was similar to the increase seen in SR-treated patients during the first year (month 0 to 12) of the trial (6.4±7.7%).[62]

The primary analysis of TROPOS (ITT, N.=4932), evaluating the effect of SR 2 g/day on non-vertebral fracture, showed a 16% RR reduction in all non-vertebral fractures over a 3-year follow-up period (RR 0.84; 95% CI 0.702-0.995; P=0.04).[49] SR treatment was associated with a 19% reduction in risk of major non-vertebral osteoporotic fractures (RR 0.81; 95% CI 0.66-0.98; P=0.031). In a post-hoc analysis requested by the regulatory authorities, the risk of hip fracture was decreased by 36% (RR 0.64; 95% CI 0.412-0.997; P=0.046) in a high-risk population (age above 74 years old, femoral-neck BMD

T-score of less than or equal to -2.4 according to National Health and Nutrition Examination Survey [NHANES] normative value).

Of the 5091 patients, 2714 (53%) completed the study up to 5 years.[48] The risk of non-vertebral fracture was reduced by 15% in the SR group compared with the placebo group (RR 0.85; 95% CI 0.73-0.99; Figure 2). A *post-hoc* analysis showed that the risk of hip fracture in a high-risk subset of the population above 74 years old and with a low femoral neck and lumbar BMD was decreased by 43% (RR 0.57; 95% CI 0.33-0.97; P=0.036), and the risk of vertebral fracture was decreased by 24% (RR 0.76; 95% CI 0.65-0.88; P<0.001) in the SR group. After 5 years, the safety profile of SR remained similar to the 3-year findings [32]).

Postmenopausal osteoporotic women having participated in the 5-year efficacy trials SOTI and TROPOS were invited to enter a 3-year open-label extension study. At the extension baseline, the population treated for 8 years (n=879; 79.1±5.6 years) had a femoral neck T-score of -2.61±0.71. The cumulative incidences of new vertebral and non-vertebral fractures (13.7% and 12%, respectively) over years 6-8 were non-statistically different from the cumulative incidences in the first 3 years of the original studies (11.5% and 9.6%). Annual relative change in lumbar spine, femoral neck and total hip BMD was significant at every visit, except the 8-year visit for femoral neck and total hip BMD. SR was safe and well tolerated over 8 years. These data indicate that the antifracture efficacy is sustained over 8 years.[63]

To assess the efficacy of SR according to the main determinants of vertebral fracture risk (age, baseline BMD, prevalent fractures, family history of osteoporosis, baseline BMI, and addiction to smoking), data from SOTI and TROPOS (N.=5082) were pooled (SR 2 g/day group [N.=2536]; placebo group [N.=2546]; average age 74 years; 3-year follow-up).[64]

SR decreased the risk of both vertebral (RR 0.60; 95% CI 0.53-0.69; P<0.001) and non-vertebral (RR 0.85; 95% CI 0.74-0.99; P=0.03) fractures. The decrease in risk of vertebral fractures was 37% (P=0.003) in women aged <70 years, 42% (P<0.001) for those aged 70-80 years and 32% (P=0.013) for those aged ≥80 years. The RR of vertebral fracture was 0.28 (95% CI 0.07-0.99; P=0.045) in osteopenic and 0.61 (95% CI 0.53-0.70; P<0.001) in osteoporotic women, and baseline BMD was not a determinant of efficacy.

Among the patients included in the SOTI study, 385 were aged 50-65 years, of which 353 were eligible for assessment of the efficacy of SR on vertebral fractures according to the ITT principle.[65] Over 3 years, treatment with SR significantly reduced the risk of vertebral fracture by 43% (RR 0.57; 95% CI 0.36-0.92; P=0.019), with a 16.9% incidence of vertebral fractures in the SR group *versus* 29.6% in the placebo group. This efficacy in reducing the risk of vertebral fractures was sustained over 4 years of treatment with SR, with a reduction of 35% (RR 0.65; 95% CI 0.42-0.99; P=0.049) and an incidence of vertebral fractures of 21.6% in the SR group *versus* 32.8% in the placebo group.

To determine whether SR also reduces fractures in elderly patients, an analysis based on preplanned pooling of data from the SOTI and TROPOS trials included 1488 women between 80 and 100 years of age followed for 3 years.[66] Yearly spinal X-rays were performed in 895 patients. Only radiographically confirmed non-vertebral fractures were included. Baseline characteristics did not differ in placebo and treatment arms. In the ITT analysis, the risk of vertebral, non-vertebral and clinical (symptomatic vertebral and non-vertebral) fractures was reduced within 1 year by 59% (P=0.002), 41% (P=0.027) and 37% (P=0.012), respectively. At the end of 3 years, vertebral, non-vertebral and clinical fracture risks were reduced by 32% (P=0.013), 31% (P=0.011) and 22% (P=0.040), respectively.

After 3 years of SR 2 g/day, each percentage point increase in femoral neck and total proximal femur BMD was associated with a 3% (95% adjusted CI 1-5%) and 2% (1-4%) reduction in risk of new vertebral fracture, respectively. The 3-year changes in femoral neck and total proximal femur BMD explained 76% and 74% of the reduction in vertebral fractures observed during the treatment, respectively.

From the SOTI and TROPOS trials, bone-specific alkaline phosphatase (BALP), C-terminal propeptide of type I procollagen (PICP), serum C-terminal telopeptide (s-CTX) and urine N-terminal telopeptide of type I collagen (u-NTX) were assessed at baseline and after 3 months. 2373 women were included in this study. Multiple regression analysis showed that 3-month changes in PICP and BALP but not s-CTX nor u-NTX were significantly (P<0.001) associated with 3-year BMD changes at the lumbar spine and the femoral neck. Changes in s-CTX, PICP and BALP were significantly associated with changes in

total proximal femur BMD. Changes in biochemical markers explain less than 8% of the BMD changes. The 3-month changes in BALP, PICP s-CTX and u-NTX were not significantly associated with fracture incidence. This study showed that short-term changes in biochemical markers of bone formation are associated with future BMD changes in patients treated with SR, suggesting a bone-forming activity of this treatment, but are not appropriate to monitor the efficacy of SR at the individual level.[67]

The effects of SR and ALN on distal tibia microstructure over 2 years were compared using High Resolution-peripheral Quantitative Computed Tomography (HR-pQCT). In this pre-planned, interim, intention-to-treat analysis at 12 months, 88 osteoporotic postmenopausal women (mean age 63.7±7.4) were randomized to SR 2 g/day or ALN 70 mg/week in a double-placebo design. Treatment with SR was associated with increases in mean cortical thickness (CTh, 5.3%), cortical area (4.9%) and trabecular density (2.1%) (all P<0.001, except cortical area P=0.013). No significant changes were observed with ALN. Between-group differences in favor of SR were observed for CTh, cortical area, relative bone volume (BV/TV) and trabecular density (P=0.045, 0.041, 0.048 and 0.035, respectively). A bone mineral density (BMD) increased to a similar extent with SR and ALN at the spine (5.7% *versus* 5.1%, respectively) and total hip (3.3% *versus* 2.2%, respectively). The authors concluded that within the methodological constraints of HR-pQCT through its possible sensitivity to X-ray attenuation of different minerals, SR had greater effects than ALN on distal tibia cortical thickness and trabecular volumetric density.[68] Using the 5-year data of a randomized placebo-controlled trial of SR (Treatment of Peripheral Osteoporosis Study [TROPOS]), the hip dual-energy X-ray absorptiometry scans were analysed to determine the role of hip geometry in the risk of hip fractures (placebo group, N.=636) and to analyse the effects of SR (N.=483). The outcomes included the hip structure analysis (HSA) parameters: cross-sectional area (CSA), section modulus, cortical thickness, and buckling ratio, measured at femoral neck, intertrochanteric (IT) region, and proximal shaft. The geometric parameters associated with an increased risk of hip fracture over 5 years were IT CSA and femoral shaft cortical thickness independent of age and total-hip bone mineral density (BMD). IT cortical thickness was associated with the risk of hip fracture. Over 5 years, significant decreases in some femoral dimensions of the placebo group contrast with significant increases in SR group after adjustment for age and BMD. Differences between placebo and SR groups were no longer significant after adjustment on 5-year BMD changes. Some HSA parameters have predictive value for hip fracture risk in postmenopausal osteoporotic women. The authors concluded that SR improves some HSA parameters, through the BMD increase.[69]

In the SOTI and TROPOS trials, the incidence of adverse events and serious adverse events and withdrawals due to adverse events were similar in the SR and placebo groups.[70, 71] During the first 3 months of treatment, nausea, diarrhea, headache, dermatitis and eczema were more frequently associated with SR compared with placebo; but, thereafter, there was no difference in incidence between SR and placebo groups concerning nausea and diarrhea.

Whereas no significant increase in venous thromboembolism (VTE) was observed in any of the individual studies, in pooled data from the SOTI and TROPOS trials, there was an apparent increased risk of VTE in the SR group (0.6% *versus* 0.9% per year), although the annual incidence was similar in the SR and placebo groups in the individual trials.[46, 59]

A recently published study used the UK General Practice Research Database (GPRD) to assess the risk of several recently reported adverse events linked to the use of SR for osteoporosis in postmenopausal women.[72] Age-adjusted rate ratios for VTE, gastrointestinal disturbance, minor skin complaint and memory loss were 1.1 (95%CI 0.2-5), 3.0 (95% CI 2.3-3.8), 2.0 (95% CI 1.3-3.1) and 1.8 (95% CI 0.2-14.1), respectively. No cases of osteonecrosis of the jaw, Stevens-Johnson syndrome or drug rash with eosinophilia and systemic symptoms (DRESS) were found. In addition, a recent analysis of the UK GPRD has shown an absence of increased risk of VTE in osteoporotic patients treated with SR, by comparison with untreated patients. Furthermore, the incidence of VTE in SR-treated patients was similar with the incidence seen in patients treated with ALN, an agent that is not especially known to increase this risk.[73]

Recently, the postmarketing experience of patients treated with SR reported cases of the DRESS syndrome (<20 for 570,000 patient-years of exposure).[74] This incidence is in the vicinity of what has been previously reported as severe skin reactions

with most other currently available antiosteoporosis medications.[75] A causative link has not been firmly established, as strontium is a trace element naturally present in the human body and ranelic acid is poorly absorbed. Owing to the possible fatality linked to this syndrome, however, it seems reasonable to discontinue immediately SR and other concomitant treatment known to induce such a syndrome in case of suspicious major skin disorders occurring within 2 months of treatment initiation [76] and to introduce adapted treatment and follow up to avoid systemic symptoms.

A small but significant increase in non-fatal myocardial infarctions was recently observed when pooling all studies assessing the effect of SR in osteoporosis and osteoarthritis.[77]

The cardiac safety of the osteoporosis treatment SR was explored in the UK Clinical Practice Research Datalink. Of the 112,445 women with treated postmenopausal osteoporosis, 6487 received SR. Annual incidence rates for first definite myocardial infarction (1352 cases), myocardial infarction with hospitalization (1465 cases), and cardiovascular death (3619 cases) were 3.24, 6.13, and 14.66 per 1000 patient-years, respectively. Obesity, smoking, and cardiovascular treatments were associated with significant increases in risk for cardiac events. Current or past use of SR was not associated with increased risk for first definite myocardial infarction (odds ratio [OR] 1.05, 95% confidence interval [CI] 0.68-1.61 and OR 1.12, 95% CI 0.79-1.58, respectively), hospitalization with myocardial infarction (OR 0.84, 95% CI 0.54-1.30 and OR 1.17, 95% CI 0.83-1.66), or cardiovascular death (OR 096, 95% CI 0.76-1.21 and OR 1.16, 95% CI 0.94-1.43) *versus* patients who had never used SR.

The authors concluded that analysis in the CPD did not find evidence for a higher risk for cardiac events associated with the use of SR in postmenopausal osteoporosis.[78]

Using the Danish National Prescription Database, a recent survey identified all 3,252 patients aged 50+ who began SR in 2005-2007 and 35,606 users of other osteoporosis drugs as controls. Hospital contacts and causes of death were retrieved from national registers.

The adjusted risk of MI was not significantly increased (women: HR 1.05 [95%CI 0179-1.41, P=0.73]; men: 1.28 [0.74-2.20, P=0.38]).[79]

In the Spring of 2013, the European Medicines Agency (EMA) warned that SR should be avoided in patients with ischemic heart disease (IHD), peripheral vascular disease (PVD) or cerebrovascular disease (CVD), and in patients with uncontrolled hypertension.[77, 79]

In an extensive assessment of the risk/benefit ratio of SR in the treatment of osteoporosis, EMA recommended, in February 2014, that the use of SR should be restricted to patients from both genders, without CV contra-indications, presenting with a severe osteoporosis and for whom treatment with other anti-osteoporosis medications is contra-indicated.

The cost effectiveness of SR was compared with non-treatment in UK women using the FRAX® algorithm for fracture assessment. At a willingness-to-pay of £ 30,000 per quality-adjusted life-year (QALY), SR was generally cost effective in women with prior fracture at the threshold of osteoporosis from an age of 65 years.[80] A validated Markov microsimulation model with a Belgian healthcare cost perspective was used to assess the cost per QALY of SR compared with no treatment, on a basis of calcium/vitamin D supplementation if needed. Analyses were performed for women aged 70, 75 and 80 years, either with a BMD T-score $\leq$2.5 SD or with prevalent vertebral fractures. Parameter uncertainty was evaluated using both univariate and probabilistic sensitivity analyses. SR was cost saving at the age of 80 years in both populations. For women with a T-score $\leq$2.5 SD, the costs per QALY gained of SR were respectively € 15,096 and € 6913 at 70 and 75 years of age, while these values were € 23,426 and € 9698 for women with prevalent vertebral fractures. Sensitivity analyses showed that the results were robust over a wide range of assumptions. The authors concluded that, compared with no treatment, long-term SR treatment is cost effective for postmenopausal women.[81, 82]

The same model was used to compare SR with bisphosphonate RIS. SR appeared to be more effective and less costly than risedronate for women with osteoporosis aged over 75 years and for women with prevalent vertebral fractures aged 80 years. The cost per QALY gained of SR compared with RIS at 75 years of age was € 11,435 for women with prevalent vertebral fractures. When compared with no treatment, the costs per QALY gained of SR were € 15,588 and € 7708 at 75 and 80 years of age for women with osteoporosis; the equivalent values were € 16,518 and € 6015 for women with prevalent

vertebral fractures. Probabilistic sensitivity analyses showed that SR was generally more cost effective than RIS, in the range of 60% in all cases. The results of this study suggest that SR is a cost effective strategy, in a Belgian setting, for the treatment of postmenopausal osteoporotic women aged over 75 years.[81, 82]

Under the assumption of the same relative risk reduction in men as for women, SR was also shown to be cost-effective compared with no-treatment for male osteoporosis.[83]

The international, double-blind, randomised, placebo-controlled SR Efficacy in Knee OsteoarthrItis (SEKOIA) evaluated the effect of this medication on radiological progression of knee osteoarthritis.

Patients with knee osteoarthritis (Kellgren and Lawrence grade 2 or 3, and joint space width [JSW] 2.5-5 mm) were randomly allocated to SR 1 g/day (N.=558), 2 g/day (N.=566) or placebo (N.=559). The primary endpoint was radiographical change in JSW (medial tibiofemoral compartment) over 3 years *versus* placebo. Secondary endpoints included radiological progression, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score, and knee pain.

The intention-to-treat population included 1371 patients. Treatment with SR was associated with smaller degradations in JSW than placebo (1 g/day: -0.23 [SD 0.56] mm; 2 g/day: -0.27 [SD 0.63] mm; placebo: -0.37 [SD 0.59] mm); treatment-placebo differences were 0.14 (SE 0.04), 95% CI 0.05 to 0.23, P<0.001 for 1 g/day and 0.10 (SE 0.04), 95% CI 0.02 to 0.19, P=0.018 for 2 g/day. Fewer radiological progressors were observed with SR (P<0.001 and P=0.012 for 1 and 2 g/day). There were greater reductions in total WOMAC score (P=0.045), pain subscore (P=0.028), physical function subscore (P=0.099) and knee pain (P=0.065) with strontium ranelate 2 g/day. SR was well tolerated.

The conclusion was that treatment with SR 1 and 2 g/day is associated with a significant effect on structure in patients with knee osteoarthritis, and a beneficial effect on symptoms for SR 2 g/day.[84]

Antibodies against sclerostin (romozosumab)

Osteoblast differentiation is predominantly regulated by the WNT/β-catenin signaling (canonical WNT pathway), which, together with bone morphogenetic proteins, acts as the master regulator of osteogenesis. The recent characterization of the canonical WNT pathway in the regulation of bone modeling and remodeling provided important insights for our understanding of the pathophysiology of a number of conditions and of the mechanism of action of hormones or drugs with important effect on bone metabolism. WNT/β-catenin signaling plays a key role in bone tissue by determining the differentiation of stem cells into mature osteoblasts rather than into chondrocytes and adipocytes. Its regulation is predominantly driven by the production of two WNT signaling antagonists: sclerostin (SOST) and Dickkopf-related protein 1 (DKK1). Inactivating monoclonal antibodies against SOST appears to be an attractive strategy because SOST is the only component of the WNT pathway expressed almost exclusively by osteocytes.[85]

Preclinical studies and an early report of a clinical study suggest that inhibition of sclerostin with AMG 785, a humanized monoclonal antibody directed against SOST**,** may provide skeletal benefit for patients with osteoporosis.[86]

Six-month-old female rats were ovariectomized and left untreated for 1 year to allow for significant estrogen deficiency-induced bone loss, at which point SOST neutralizing monoclonal antibody (SOST-Ab) was administered for 5 weeks. SOST-Ab treatment in these animals had robust anabolic effects, with marked increases in bone formation on trabecular, periosteal, endocortical, and intracortical surfaces. This not only resulted in complete reversal, at several skeletal sites, of the 1 year of estrogen deficiency-induced bone loss, but also further increased bone mass and bone strength to levels greater than those found in non-ovariectomized control rats.[87]

Sixteen-month-old male Sprague-Dawley rats were injected subcutaneously with vehicle or SOST-Ab at 5 or 25 mg/kg twice per week for 5 weeks (9-10/group). In vivo dual-energy X-ray absorptiometry (DXA) analysis showed that there was a marked increase in areal bone mineral density of the lumbar vertebrae (L1 to L5) and long bones (femur and tibia) in both the 5 and 25 mg/kg SOST-Ab -treated groups compared with baseline or vehicle controls at 3 and 5 weeks after treatment. Ex vivo microcomputed tomographic (mCT) analysis demonstrated improved trabecular and cortical architecture at the fifth lumbar vertebral body (L5), femoral diaphysis (FD), and femoral neck (FN) in both SOST-Ab dose groups

compared with vehicle controls. The increased cortical and trabecular bone mass was associated with a significantly higher maximal load of L5, FD, and FN in the high-dose group. These results indicate that sclerostin inhibition by treatment with a sclerostin antibody increased bone formation, bone mass, and bone strength in aged male rats. This suggests that pharmacologic inhibition of sclerostin may represent a promising anabolic therapy for low bone mass in aged men.[88]

To explore the effects of sclerostin inhibition in primates, SOST-Ab was administered to gonad-intact female cynomolgus monkeys. Two once-monthly subcutaneous injections of SOST-Ab were administered at three dose levels (3, 10, and 30 mg/kg), with study termination at 2 months. SOST-Ab treatment had clear anabolic effects, with marked dose-dependent increases in bone formation on trabecular, periosteal, endocortical, and intracortical surfaces. Bone densitometry showed that the increases in bone formation with SOST-Ab treatment resulted in significant increases in bone mineral content (BMC) and/or bone mineral density (BMD) at several skeletal sites (*i.e.*, femoral neck, radial metaphysis, and tibial metaphysis). Additionally, significant increases in trabecular thickness and bone strength were found at the lumbar vertebrae in the highest-dose group.[89]

In the first-in-human study, the SOST-Ab (AMG 785) was administered to healthy men and postmenopausal women. In this phase I, randomized, double-blind, placebo-controlled, ascending, single-dose study, 72 healthy subjects received AMG 785 or placebo (3:1) subcutaneously (0.1, 0.3, 1, 3, 5, or 10 mg/kg) or intravenously (1 or 5 mg/kg). Depending on dose, subjects were followed for up to 85 days. The effects of AMG 785 on safety and tolerability (primary objectives) and pharmacokinetics, bone turnover markers, and bone mineral density (secondary objectives) were evaluated. AMG 785 generally was well tolerated. One treatment-related serious adverse event of nonspecific hepatitis was reported and was resolved. No deaths or study discontinuations occurred. AMG 785 pharmacokinetics were non-linear with dose. Dose-related increases in the bone-formation markers procollagen type 1 N-propeptide (P1NP), bone-specific alkaline phosphatase (BAP), and osteocalcin were observed, along with a dose-related decrease in the bone-resorption marker serum C-telopeptide (sCTx), resulting in a large anabolic window. In addition, statistically significant increases in bone mineral density of up to 5.3% at the lumbar spine and 2.8% at the total hip compared with placebo were observed on day 85. Six subjects in the higher-dose groups developed anti-AMG 785 antibodies, 2 of which were neutralizing, with no discernible effect on the pharmacokinetics or pharmacodynamics.[90]

These preclinical results suggested that antibody-mediated inhibition of sclerostin represents a promising new therapeutic approach for the anabolic treatment of bone-related disorders, such as postmenopausal osteoporosis.

The effects of systemic administration of SOST-Ab were investigated in two models of fracture healing. In both, a closed femoral fracture model in rats and a fibular osteotomy model in cynomolgus monkeys, SOST-Ab significantly increased bone mass and bone strength at the site of fracture. After 10 weeks of healing in non-human primates, the fractures in the SOST-Ab group had less callus cartilage and smaller fracture gaps containing more bone and less fibrovascular tissue. These improvements at the fracture site corresponded with improvements in bone formation, bone mass, and bone strength at non fractured cortical and trabecular sites in both studies. Thus, the authors concluded that the potent anabolic activity of SOST-Ab throughout the skeleton also was associated with an anabolic effect at the site of fracture. These results support the potential for systemic SOST-Ab administration to enhance fracture healing in patients.[91]

In a phase 2, multicenter, international, randomized, placebo-controlled, parallel-group, eight-group study, the efficacy and safety of romosozumab (SOST-Ab), formerly called AMG-785, was evaluated over a 12-month period in 419 postmenopausal women, 55 to 85 years of age, who had low bone mineral density (a T score of -2 or less at the lumbar spine, total hip, or femoral neck and -3.5 or more at each of the three sites). Participants were randomly assigned to receive subcutaneous romosozumab monthly (at a dose of 70 mg, 140 mg, or 210 mg) or every 3 months (140 mg or 210 mg), subcutaneous placebo, or an open-label active comparator – oral alendronate (70 mg weekly) or subcutaneous teriparatide (20 μg daily). All dose levels of romosozumab were associated with significant increases in bone mineral density at the lumbar spine, including an increase of 11.3% with the 210-mg monthly dose, as compared with a decrease of 0.1% with placebo and increases of 4.1% with alendronate

and 7.1% with teriparatide. Romosozumab was also associated with large increases in bone mineral density at the total hip and femoral neck, as well as transitory increases in bone-formation markers and sustained decreases in a bone-resorption marker. Except for mild, generally nonrecurring injection-site reactions with romosozumab, adverse events were similar among groups. The authors concluded that in postmenopausal women with low bone mass, romosozumab was associated with increased bone mineral density and bone formation and with decreased bone resorption.[92]

A large phase III program assessing antifracture efficacy of romosozumab as well as its long-term safety is currently ongoing.

Conclusions

During many years, inhibitors of bone resorption were the only option for the treatment of osteoporosis. However, there was an unmet medical need, for patients who were poor responders to antiresorptive agents, who had a limited compliance to these medications or who were presenting with drug-induced adverse events. Chemical entities with the potential or preferentially stimulating osteoblast number, lifespan or activity, or capable of uncoupling bone formation from bone resorption were progressively developed.

Peptides from the parathyroid hormone family and strontium ranelate were shown to significantly reduce fracture rates but strontium ranelate is no longer an option for treating osteoporosis because of its safety profile. New therapeutic options, including monoclonal antibodies against sclerostin seem to be promising but their role in the armamentarium of osteoporosis will depend on the results of the current phase 3 study, assessing their antifracture efficacy and long-term safety.

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