

# The Treatment of Severe Postmenopausal Osteoporosis

## A Review of Current and Emerging Therapeutic Options

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### Abstract

Several chemical entities have shown their ability to reduce axial and/or appendicular fractures in patients with osteoporosis. Since patients who have experienced a previous fracture are at high risk for subsequent vertebral or hip fracture, it is of prime importance to treat such patients with medications that have unequivocally demonstrated their ability to reduce fracture rates in patients with prevalent fractures. Results obtained with calcium and vitamin D, in this particular population, are not fully satisfactory and these medications are probably better used in conjunction with other therapeutic regimens. Bisphosphonates have shown their ability to reduce vertebral (alendronate, risedronate, ibandronate) and non-vertebral (alendronate, risedronate) fractures in patients with established osteoporosis. Raloxifene has also shown similar properties, notwithstanding its effect on non-vertebral fractures, which has only been derived from a *post-hoc* analysis limited to patients with prevalent severe vertebral fractures at baseline. This compound also has interesting non-skeletal benefits, including effects on the breast and heart. Teriparatide, a bone-forming agent, promptly reduces the rate of vertebral and all non-vertebral fractures, without significant adverse effects. Strontium ranelate, the first agent shown to concomitantly decrease bone resorption and stimulate bone formation, has also shown its ability to reduce rates of vertebral and non-vertebral fractures in patients with established osteoporosis. It significantly reduces hip fractures in elderly individuals at high risk for such events. Its safety profile is also excellent.

Osteoporosis is characterized by bone fragility due to low bone mass and modifications of the internal bone structure, with alterations of its micro-architecture.<sup>[1]</sup> Low bone mineral density (BMD) is considered the single best predictor of risk for an individual to subsequently present with an osteoporotic fracture. Consequently,

the WHO defines osteoporosis as a condition characterized by a BMD value at least 2.5 standard deviations below the mean for a young healthy population (BMD T-score less than -2.5). In the presence of a BMD T-score less than -2.5 and a prevalent fracture, the condition is called severe or established osteoporosis.<sup>[1]</sup> Of the

various fragility fractures, which represent the major complication of the disease, vertebral and hip fractures are associated with pronounced morbidity and increased mortality.<sup>[1]</sup> Only one-third of all radiologic vertebral fractures (morphometric fractures) generate symptoms (clinical vertebral fractures). In the appendicular skeleton, fractures occurring at the clavicle, humerus, wrist, pelvis, hip, and lower leg are considered major non-vertebral fractures. Although several agents have been used for many years to prevent or treat osteoporosis, methodologically sound, randomized controlled trials assessing anti-fracture efficacy at axial (vertebral) and appendicular (non-vertebral) sites of the skeleton have only become available within the last 15 years. Most of these trials have recently been summarized in evidence-based<sup>[1-3]</sup> or quantitative systematic (meta-analysis) reviews.<sup>[4]</sup> People who have had one fracture are at high risk of another. It seems, therefore, important to provide these individuals with treatments that have unequivocally demonstrated their ability to reduce fracture risk, in the presence of prevalent vertebral or non-vertebral fractures.

This article reviews the pharmacologic treatment options for severe postmenopausal osteoporosis and secondary fracture prevention. It summarizes the available clinical evidence with respect to safety and efficacy of both currently available and emerging agents for the treatment of patients with severe disease. We based our review on studies published between 1975 and 2005 that reported results, with a follow-up of at least 1 year, of the radiologic or clinical evidence of fracture.

## 1. Calcium and Vitamin D

Calcium and/or vitamin D deficiency is associated with secondary hyperparathyroidism, increased bone turnover, and bone loss with increased fracture risk. Calcium deficiency is most often linked to inadequate intake of dietary calcium, while factors that contribute to low vitamin D levels include low exposure to sunlight, decreased synthesis in skin, and reduced intestinal absorption related to aging and limited dietary sources.<sup>[5]</sup> Whereas several randomized controlled trials and/or meta-analyses have been performed to assess the efficacy and safety of calcium and/or vitamin D supplementation in the prevention of osteoporotic fractures in elderly individuals, few of them were designed to answer this question in individuals who had already experienced a previous fracture. Between 1975 and 2004, only two studies assessed incident fracture rates in women with severe osteoporosis receiving calcium supplementation. In women over the age of 60 years with prevalent vertebral fractures who were consuming <1 g/day of calcium, supplementation with calcium carbonate 1200 mg/day

reduced incident radiographic vertebral fractures (relative risk [RR] 0.58; 95% CI 0.3, 0.97) after a mean duration of 4.3 years.<sup>[6]</sup> In vitamin D-replete elderly patients (mean age 78.4 years) with a previous hip fracture, a daily intake of calcium 800 mg/day in two different forms yielded incident rates of new vertebral fractures of 100% and 50% above those observed in women without prevalent fractures, regardless of whether they were receiving calcium supplementation. Whereas the authors concluded that oral calcium supplementation lowered fracture rates in elderly patients, the design of the study (which lacked a placebo treatment group in patients with hip fractures) makes it difficult to extrapolate this statement to women with previous hip fractures.<sup>[7]</sup>

A recently published study, RECORD (Randomized Evaluation of Calcium OR vitamin D), addressed specifically this issue by assigning a large cohort of people aged 70 years or older, who were mobile before developing a low-trauma fracture, to oral colecalciferol 800 IU/day, calcium 1000 mg/day, both of these agents, or a placebo, for a follow-up that varied between 24 months and 62 months. The incidence of new low-trauma fracture did not differ between patients who were receiving calcium and those who were not (hazard ratio [HR] 0.94; 95% CI 0.81, 1.09), those receiving colecalciferol or not (HR 1.02; 95% CI 0.88, 1.19), and those receiving the combination treatment or placebo (HR 1.01; 95% CI 0.75, 1.36).<sup>[8]</sup> However, it should be noted that, in the RECORD study, the compliance with medication was poor. It declined to 63% after 2 years and might have been as low as 45% when non-responders to the questionnaire about compliance were included. Compliance and adherence are widely recognized as major factors affecting outcomes in osteoporosis management, and extreme caution should be used when extrapolating the results of the RECORD study to other settings where the adherence would be better.<sup>[9]</sup>

Calcium and/or vitamin D supplementation has been repeatedly<sup>[10,11]</sup> but not systematically<sup>[12]</sup> suggested to be an effective way to reduce osteoporotic fractures (mainly at non-vertebral sites) in elderly patients at increased risk; however, similar positive effects have not been clearly established in patients with prevalent fractures. Currently available results are more supportive of their use in combination with another therapeutic regimen in this particular indication.<sup>[12]</sup>

## 2. D-Hormones (Active Metabolites of Vitamin D)

Alfacalcidol [ $1-\alpha(\text{OH})\text{D}_3$ ] and calcitriol [ $1,25(\text{OH})_2\text{D}_3$ ] have been investigated for more than 2 decades in patients with severe osteoporosis but, in most studies, the methodology used either for

selection of patients or for the assessment of the fracture outcomes makes it rather difficult to draw unequivocal conclusions.<sup>[13]</sup>

In Japanese women (mean age 71.9 years), with low bone mass and prevalent fractures at baseline, 1 µg/day of alfacalcidol reduced new vertebral fracture rates after 1 year. However, the control patients had 1.89 fractures/patient at baseline whereas the treated patients had only 1.24 fractures/patient at baseline.<sup>[14]</sup> Consequently, some of the observed differences between the groups may be attributed to baseline differences in fracture susceptibility between the treatment and placebo groups, rather than to the effects of the treatment.<sup>[15]</sup> A recent re-analysis of the results of this study did not reach similar conclusions and questioned the axial (RR 0.37; 95% CI 0.09, 1.44) and appendicular (RR 1.10; 95% CI 0.02, 2) anti-fracture efficacies of alfacalcidol.<sup>[16]</sup> Another Japanese study showed a positive effect of alfacalcidol (1 µg/day) on vertebral fracture rates (RR 0.46; 95% CI 0.31, 0.69) but the information provided in the original publication<sup>[17]</sup> does not authoritatively confirm the prevalence of fractures in all individuals at baseline. Pharmacologic management of established osteoporosis with calcitriol yielded conflicting results. A mean dosage of 0.43 µg/day given to postmenopausal women with vertebral compression fractures did not provide a significant benefit compared with placebo (RR for new vertebral fracture 1.46; 95% CI 0.59, 3.62 and RR for non-vertebral fracture 2.20; 95% CI 0.52, 9.24) after 2 years.<sup>[16,18]</sup> In addition, no differences between the groups were observed for vertebral fractures in a study assessing calcitriol (dose adjusted to maintain serum calcium <11 mg/dL) in women with vertebral fractures (RR 0.90; 95% CI 0.42, 1.83).<sup>[19]</sup> However, these two studies were largely underpowered to assess an effect of the tested medication on fracture rates (including  $n = 86$ <sup>[18]</sup> and  $n = 50$ <sup>[19]</sup> patients, respectively). In a larger single-blind, randomized controlled trial ( $n = 622$ ), women who received calcitriol (0.50 µg/day) and calcium (1 g/day) for 3 years had fewer fractures than those who received calcium alone. The reduction in vertebral fracture rate was significant (RR 0.43; 95% CI 0.31, 0.61) overall, but mainly driven by an unexplained increase in fracture rates observed during the second and third years in women receiving calcium alone. This beneficial effect of calcitriol was evident only in women who had no more than five vertebral fractures at baseline. The author claimed a significant difference in the number of peripheral fractures but further reassessment of the results showed this to be of only borderline statistical significance (RR 0.50; 95% CI 0.25, 1).<sup>[16,20]</sup>

The respective beneficial effects of native or hydroxylated forms of vitamin D were not directly compared in women with prevalent fractures. However, considering all trials reporting frac-

ture outcomes in primary osteoporosis<sup>[21]</sup> or in older people,<sup>[22]</sup> two recent meta-analyses yielded conflicting results, suggesting either a lower adjusted global RR for fracture when patients were allocated to hydroxylated forms<sup>[21]</sup> or no evidence of advantages of the D-hormone compared with native vitamin D.<sup>[22]</sup> The latter meta-analysis concluded that the risk of hypercalcemia was particularly high with calcitriol (RR 14.94; 95% CI 2.95, 75.61) compared with placebo or calcium. There was no evidence that vitamin D (plain or hydroxylated) increased gastrointestinal symptoms (RR 1.03; 95% CI 0.79, 1.36) or renal disease (RR 0.80; 95% CI 0.34, 1.87).<sup>[22]</sup>

A number of results, either from randomized controlled trials or meta-analyses, suggest that active vitamin D metabolites, mainly alfacalcidol, may exert a preventive effect on fracture recurrence in women with established osteoporosis. Besides their actions through the classical pathway of interfering with bone strength, some recent data also suggested that alfacalcidol might reduce the propensity of elderly individuals to fall.<sup>[23]</sup>

### 3. Calcitonin

Calcitonin is an endogenous polypeptidic hormone that inhibits osteoclastic bone resorption.<sup>[2]</sup> The vast majority of clinical trials have been performed with salmon calcitonin, which is 40–50 times more potent than human calcitonin.<sup>[2]</sup> Most of the initial studies using injectable<sup>[24,25]</sup> or intranasal<sup>[26,27]</sup> salmon calcitonin that were performed in women with established osteoporosis were of insufficient size to draw significant conclusions. The PROOF (Prevent Recurrence Of Osteoporotic Fracture) study randomized 1255 women with prevalent fractures to salmon calcitonin nasal spray (100, 200, or 400 IU/day) or placebo for 5 years. Despite an important proportion of patients lost to follow-up (59.3%), the PROOF study concluded that there was a borderline significant reduction in vertebral fracture rates (RR 0.79; 95% CI 0.62, 1) for the 200 IU/day group, while no significant effects were observed for the 100 IU/day and 400 IU/day groups.<sup>[28]</sup> With regard to non-vertebral fractures, the pooled effect did not reach statistical significance (RR 0.80; 95% CI 0.59, 1.09). The absence of a clearcut dose dependence for fracture prevention is a seriously troubling feature in this study. Generally speaking, the tolerance of nasal salmon calcitonin was good but the reporting of adverse events was rather poor.<sup>[2,28]</sup> A recent meta-analysis suggested a non-significant increase in rhinitis (RR 1.72; 95% CI 0.92, 3.23) in treated patients.<sup>[29]</sup>

Calcitonin is likely to reduce the risk of vertebral fractures in patients with established osteoporosis. However, the marginal

effect size of the reduction, the absence of proven efficacy against non-vertebral fractures, and the prohibitive costs of the nasal formulation make its interest at least questionable.

#### 4. Selective Estrogen Receptor Modulators

Selective estrogen receptor modulators are non-hormonal compounds that have the property of binding to estrogen receptors in various tissues. They behave like estrogen agonists towards some target tissues (e.g. bone, liver), but they exert an estrogen antagonistic action on the breast and/or (according to the drug) an action on other female sexual organs, such as the uterus, that may or may not be agonistic.

In the MORE (Multiple Outcomes of Raloxifene Evaluation) study,<sup>[30]</sup> 7705 postmenopausal women (who were at least 2 years' postmenopausal) received raloxifene 60 mg/day or 120mg/day or placebo. All women received calcium (500 mg/day) and vitamin D (400 IU/day) supplementation. The main endpoint of MORE was the reduction in the percentage of women developing a new vertebral fracture when receiving raloxifene. The secondary endpoints assessed the RR for non-vertebral fractures, breast cancer, and cardiovascular events. After the 3-year study period, the RR of incident vertebral fracture was significantly decreased in women with prevalent vertebral fractures (RR 0.70; 95% CI 0.56, 0.86).<sup>[30]</sup> Raloxifene, at a dosage of 60 mg/day, reduced the risk of incident clinical vertebral fracture by 66% during the first year of therapy (RR 0.34; 95% CI 0.11, 0.77) in the group of women with prevalent vertebral fractures.<sup>[31]</sup> The risk of a non-vertebral fracture was not significantly different between the group of patients treated with either raloxifene 60 mg/day or 120 mg/day and those treated with placebo (RR 0.9; 95% CI 0.8, 1.1). However, in a *post-hoc* analysis, a subgroup of patients who had a severe vertebral fracture (semi-quantitative grade 3) before starting the study (n = 614) experienced a significant decrease in the risk of non-vertebral fractures within the 3 years of the study. In this group with severe osteoporosis, raloxifene 60 mg/day allowed a reduction of 26% in the risk of new vertebral fracture (RR 0.74; 95% CI 0.54, 0.99) and a reduction of 47% in the non-vertebral fracture risk (clavicle, humerus, wrist, pelvis, hip, and leg) [RR 0.53; 95% CI 0.29, 0.99].<sup>[32]</sup> During the 3 years of the MORE study, raloxifene led to a significant 37% decrease (RR 0.63; 95% CI 0.49, 0.83) in the occurrence of one new moderate or severe vertebral fracture in women with at least one prevalent vertebral fracture before initiation of therapy.<sup>[33]</sup> Moreover, the extension of the MORE study to a fourth year confirmed the persistence of the anti-

fracture efficacy of raloxifene 60 mg/day. During the fourth year, if results in the fourth year were considered separately, the risk of a new vertebral fracture was reduced by 48% (RR 0.52; 95% CI 0.35, 0.78) in patients who had a prevalent vertebral fracture before starting the study.<sup>[34]</sup>

The MORE study was continued for an additional 4 years (CORE [Continuing Outcomes Relevant to Evista]). The risk of at least one new non-vertebral fracture was similar in the placebo (22.9%) and raloxifene (22.8%) groups. The incidence of at least one new non-vertebral fracture at six major sites (clavicle, humerus, wrist, pelvis, hip, lower leg) was 17.5% in both groups. However, a decreased risk at six major non-vertebral sites was seen in women with prevalent vertebral fractures (RR 0.78; 95% CI 0.63, 0.96).<sup>[35]</sup> Some extraskeletal effects have been observed with raloxifene. After 3 years of therapy, 13 cases of breast cancer developed in the 5129 women receiving raloxifene versus 27 cases in the 2576 women receiving placebo (RR 0.24; 95% CI 0.13, 0.44). Raloxifene reduced the risk of estrogen receptor-positive breast cancer by 90% (RR 0.10; 95% CI 0.04, 0.24), but did not reduce the risk of estrogen receptor-negative invasive breast cancer (RR 0.88; 95% CI 0.26, 3).<sup>[36]</sup> In the MORE study, there was no significant difference in the incidence of combined coronary and cerebrovascular complications between raloxifene and placebo recipients in the overall cohort. However, in 1035 women with increased cardiovascular risk at baseline, a decrease of 40% in the risk of cardiovascular complications was observed in those receiving raloxifene (RR 0.60; 95% CI 0.38, 0.95).<sup>[37]</sup> Hot flashes were the most frequent adverse effect, leading to withdrawal from therapy in 0.1%, 0.7%, and 0.5% of women receiving placebo, raloxifene 60mg, and raloxifene 120mg, respectively. Leg cramps were more frequent in those women receiving raloxifene (7% in the 60mg group and 6.9% in the 120mg group) than in those receiving placebo (3.7%).<sup>[30]</sup> After 3 years, raloxifene was associated with an increased risk of venous thromboembolic complications (RR 3.1; 95% CI 1.5, 6.2) but did not increase the risk of endometrial cancer (RR 0.8; 95% CI 0.2, 2.7).<sup>[30]</sup>

Raloxifene at the dosage of 60 mg/day, the dose approved for therapy, is able to prospectively produce a significant decrease in the vertebral fracture risk in postmenopausal women with established osteoporosis.<sup>[2,30]</sup> There are some convergent, but retrospective, data tending to demonstrate that raloxifene could also prevent non-vertebral fractures in patients with severe osteoporosis.<sup>[32]</sup> Raloxifene might also confer some extraskeletal advantages, such as prevention of breast cancer and cardiovascular events.<sup>[36,37]</sup>



## 5. Bisphosphonates

Bisphosphonates are synthetic analogs of the naturally occurring pyrophosphates. Bisphosphonates localize preferentially to sites of active bone remodeling.<sup>[2]</sup> They act directly on mature osteoclasts, decreasing their bone resorption activity. Moreover, bisphosphonates can induce osteoclast apoptosis.<sup>[2]</sup>

Etidronate is administered intermittently (400 mg/day for 2 weeks every 3 months) for 3–5 years. Several studies of similar design have examined the anti-fracture efficacy of cyclical etidronate in postmenopausal women with prevalent vertebral fractures.<sup>[2]</sup> Methodologic problems with fracture assessment, limited statistical power, potential toxicity of the compound with regard to bone mineralization, the necessity to perform *post-hoc* analyses to show an effect regarding the prevention of new vertebral fractures in postmenopausal women with low bone mass, and patients with multiple prevalent vertebral fractures led to the conclusion that etidronate was a largely obsolete form of therapy.<sup>[2]</sup>

Oral alendronate for the treatment of osteoporosis has been extensively studied under randomized controlled trial conditions. In an initial 3-year study, alendronate significantly increased BMD and reduced the incidence of new vertebral deformities when given in different doses to osteoporotic women, 20% of whom had prevalent vertebral deformities.<sup>[38]</sup> At the end of 3 years, one or more new vertebral fractures had occurred in 6.2% of women in the placebo group and in 3.2% of women treated with alendronate. Alendronate reduced the vertebral fracture rate by 48% (RR 0.52; 95% CI 0.28, 0.95).<sup>[38]</sup> The anti-fracture efficacy of alendronate has been best established in two large populations of postmenopausal women, one with and one without pre-existing vertebral fractures.<sup>[2,39]</sup> The daily dose of alendronate was 5mg for the first 2 years and 10mg thereafter. In the study including 2027 women with established osteoporosis (i.e. with at least one prevalent vertebral fracture at baseline), alendronate reduced the incidence of new vertebral fractures by 47% (RR 0.53; 95% CI 0.41, 0.68). The incidence of vertebral fractures with clinical symptoms was similarly reduced (RR 0.46; 95% CI 0.28, 0.75). There was no reduction in the overall risk of non-vertebral fractures (RR 0.80; 95% CI 0.63, 1.01), but hip fracture incidence was also reduced (RR 0.49; 95% CI 0.23, 0.99) as was wrist fracture risk (RR 0.52; 95% CI 0.31, 0.87).<sup>[39]</sup>

Daily compliance with 10mg of alendronate is uncertain and difficult to maintain in routine clinical practice. The efficacy and safety of treatment with oral, once-weekly alendronate 70mg, twice-weekly alendronate 35mg, and daily alendronate 10mg have

been compared in a double-blind, 1-year study involving a total of 1258 postmenopausal osteoporotic women.<sup>[40]</sup> This study included both patients with low BMD and patients with prevalent vertebral or hip fractures. The increases in BMD at the lumbar spine, hip, and total body were similar for the three regimens and the fall in bone turnover markers was also quite similar. The gastrointestinal tolerability of the once-weekly regimen and daily administration were similar.<sup>[40]</sup> The anti-fracture efficacy of the weekly formulation is assumed to be similar to that of the daily formulation, but this has not been formally tested.

Risedronate efficacy has been extensively tested in double-blind, placebo-controlled trials. Risedronate at a dosage of 5 mg/day for 3 years has thus been shown to significantly reduce the vertebral fracture risk in established osteoporosis compared with placebo.<sup>[41,42]</sup> In women with at least one vertebral fracture at baseline, the relative reduction in new vertebral fractures was 41% (RR 0.59; 95% CI 0.42, 0.82), and a 39% reduction was seen for non-vertebral fractures (RR 0.61; 95% CI 0.39, 0.94).<sup>[41]</sup> In women with at least two vertebral fractures at baseline, the risk of new vertebral fractures was reduced by 49% (RR 0.51; 95% CI 0.36, 0.73) but, in this study, the effect on new non-vertebral fractures was not significant (RR 0.67; 95% CI 0.44, 1.04).<sup>[42]</sup> In both studies, the effect on the vertebral fracture rate was significant after 1 year. Pooling of both studies showed that after 1 year of treatment, the risk of new vertebral fractures was reduced by 62% (RR 0.38; 95% CI 0.25, 0.56) and the risk of multiple new vertebral fractures was reduced by 90% (RR 0.10; 95% CI 0.04, 0.26).<sup>[43]</sup> The European study<sup>[41]</sup> was continued blindly in a subset of the population and the anti-fracture efficacy was maintained for at least 5 years.<sup>[44]</sup> More recently, vertebral fracture risk reduction with risedronate was confirmed in women aged >80 years with documented osteoporosis (RR 0.56; 95% CI 0.39, 0.81).<sup>[45]</sup> The vertebral fracture efficacy of risedronate has recently been shown to be largely independent of the presence of clinical risk factors for osteoporotic fractures.<sup>[46]</sup>

Risedronate has also been shown to decrease the incidence of hip fractures in a controlled trial specifically designed for that purpose.<sup>[47]</sup> However, hip fracture reduction was only observed in women with documented osteoporosis. In this placebo-controlled study involving 5445 women aged 70–79 years who had osteoporosis and risk factors for falls, it was shown that risedronate 2.5 mg/day or 5 mg/day for 3 years (the actual mean duration of treatment was 2 years) lowered the risk of hip fracture by 40% (RR 0.6; 95% CI 0.4, 0.9). There was no dose effect and, interestingly, the effect was greater in the group of women who had a vertebral fracture at baseline (RR 0.4; 95% CI 0.2, 0.8). However, in the

same study there was no significant effect of risedronate in 3886 women aged  $\geq 80$  years (RR 0.8; 95% CI 0.6, 1.2), but these patients were essentially selected on the basis of the presence of at least one risk factor for hip fracture, such as difficulty standing from a sitting position or a poor tandem gait, rather than on the basis of low BMD or prevalent fractures.<sup>[47]</sup>

Like alendronate, risedronate has also shown a good safety profile in clinical trials.<sup>[1,2]</sup> The safety profile of risedronate was similar to that of placebo, despite the fact that, unlike in the alendronate trials, patients with a history of gastrointestinal disease or long-term use of NSAIDs were not excluded from the risedronate studies. A weekly formulation of risedronate has also been developed and, as for alendronate, has been shown to be therapeutically equivalent to the daily formulation as judged by the effects on bone density and on bone turnover.<sup>[48]</sup>

A large, 3-year, multinational, double-blind, placebo-controlled, phase III, fracture prevention study (BONE [ibandronate Osteoporosis vertebral fracture trial in North America and Europe])<sup>[49]</sup> explored the efficacy and safety of daily (2.5mg) and intermittent (between course interval  $>2$  months; 20mg every other day for 12 doses every 3 months) oral ibandronate in the treatment of postmenopausal osteoporosis. The BONE study enrolled 2946 postmenopausal women with a BMD T-score at the lumbar spine of less than or equal to  $-2$  and one to four prevalent vertebral fractures. Both regimens were similarly effective and significantly reduced the rate of new morphometric vertebral fractures by 62% (RR 0.38; 95% CI 0.25, 0.59) and 50% (RR 0.50; 95% CI 0.34, 0.74), respectively, versus placebo; the difference between the two treatment regimens was not statistically significant. As well as reducing the risk of new morphometric vertebral fractures, oral daily and intermittent ibandronate reduced the risk of new and worsening vertebral fractures (62% and 50%, respectively) to a statistically significant extent and decreased the risk of new clinical vertebral fractures (by 49% and 48%, respectively), relative to placebo, after 3 years.<sup>[49]</sup>

The overall population was at a low risk for osteoporotic fractures. Consequently, the incidence of non-vertebral fractures was similar between the ibandronate and placebo groups after 3 years (9.1%, 8.9%, and 8.2% in the daily, intermittent, and placebo groups, respectively; difference between arms not significant). A *post-hoc* analysis reported a 69% reduction in non-vertebral fractures in the daily treatment group when considering high-risk patients with a femoral neck T-score less than  $-3$ .<sup>[50]</sup>

A monthly oral formulation of ibandronate (150mg) was recently shown to be highly effective in decreasing bone turnover<sup>[51]</sup> and increasing BMD,<sup>[52]</sup> suggesting a potential role for once-

monthly oral ibandronate in the treatment of postmenopausal osteoporosis.

Bisphosphonates have been shown to reduce vertebral fractures (alendronate, risedronate, ibandronate) and hip fractures (alendronate, risedronate) in women with established osteoporosis (low BMD and prevalent fractures). There is currently no compelling evidence for significant differences in the magnitude of treatment effects between bisphosphonates.

## 6. Peptides from the Parathyroid Hormone Family

Peptides from the parathyroid hormone (PTH) family have been investigated in the management of osteoporosis for more than 30 years. 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.<sup>[1,2,53]</sup> However, daily 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.

In order to assess the effects of teriparatide (the 1–34 amino-terminal fragment of PTH) on fractures, 1637 postmenopausal women with prior vertebral fractures were randomly assigned to receive 20 $\mu$ g or 40 $\mu$ g of teriparatide or placebo, self-administered subcutaneously daily.<sup>[53]</sup>

New vertebral fractures occurred in 14% of women in the placebo group and in 5% and 4%, respectively, of women in the 20 $\mu$ g and 40 $\mu$ g dose groups. The RRs for fracture compared with the placebo group were 0.35 and 0.31 (95% CI 0.22, 0.55 and 0.19, 0.50), respectively. New non-vertebral fragility fractures occurred in 6% of women in the placebo group and 3% of women in each teriparatide group (RR 0.47 and 0.46; 95% CI 0.25, 0.88 and 0.25, 0.86, respectively).

Teriparatide had only minor side effects (occasional nausea and headache).<sup>[53]</sup>

The anti-fracture efficacy of teriparatide with regard to the spine was not modulated by the age of the individuals ( $<65$  years, 65–75 years, or  $>75$  years), prevalent spinal BMD values (T-score less than or equal to  $-2.5$  or greater than or equal to  $-2.5$ ), or the number of prevalent fractures (one or two or more fractures).<sup>[54]</sup>

At the end of this trial, patients were followed for an additional 18-month period without teriparatide, during which they were allowed to use any anti-osteoporotic medication considered appropriate by their caregiver. While the proportion of patients who

received an inhibitor of bone resorption was slightly higher among those previously in the placebo group than those who received 20 µg/day of teriparatide, the reduction of non-vertebral fractures observed in the teriparatide group during the initial trial was confirmed during the 18-month period of follow-up (RR 0.59; 95% CI 0.42, 0.85).<sup>[55]</sup> All participants in this trial were invited to participate in an additional follow-up, to assess non-vertebral fragility fractures for an overall 50-month period including treatment and follow-up. The HR for non-vertebral fragility fractures in each teriparatide group relative to placebo was statistically significant for the 50-month period (20 µg/day: HR 0.62; 95% CI 0.41, 0.93 and 40 µg/day: HR 0.52; 95% CI 0.34, 0.82). In the follow-up period, the HR indicated a significant difference between the 40µg group versus the placebo group but not between the 20µg group versus the placebo group. However, the 20µg and 40µg groups were not significantly different from each other. The analysis of time to fracture showed that the fracture incidence in the former placebo and teriparatide groups diverged during the 50-month period that included teriparatide treatment and follow-up ( $p = 0.009$ ).<sup>[56]</sup>

Treatment of postmenopausal osteoporosis with teriparatide decreases the risk of vertebral and non-vertebral fractures, and is well tolerated. The 40µg dose increases BMD more than the 20µg dose but has similar effects on the risk of fractures and is more likely to have adverse effects (such as transient hypercalcemia, which was of no concern with the 20 µg/day dosage).

## 7. Strontium Ranelate

Strontium ranelate appears to have a particular profile characterized by an inhibition of bone resorption and a stimulation of bone formation, suggesting that, for the first time, a chemical entity used in the treatment of osteoporosis could be targeted to an uncoupling of the bone remodeling process.

Strontium ranelate has been investigated in a large phase III program that included two extensive clinical trials in the treatment of severe osteoporosis: SOTI (Spinal Osteoporosis Therapeutic Intervention) and TROPOS (TReatment Of Peripheral Osteoporosis) aimed at evaluating the effect of strontium ranelate on spinal and peripheral (non-spinal) fractures.<sup>[17,57]</sup> Both studies were randomized, double-blind, placebo-controlled and multinational with two parallel groups (strontium ranelate 2 g/day vs placebo), with a study duration of 5 years, with the main statistical analysis planned after 3 years.

All patients included in these two studies had previously participated in a normalization of calcium and vitamin D study called

FIRST (Fracture International Run-in Strontium ranelate Trials). Throughout the studies, the patients received calcium/vitamin D supplements that were individually adapted according to their deficiencies (500mg or 1000mg of calcium, and 400IU or 800IU of colecalciferol). From more than 9000 osteoporotic postmenopausal women who took part in FIRST, 1649 patients were included in SOTI, with a mean age of 69 years, and 5091 patients were included in TROPOS, with a mean age of 77 years.<sup>[57,58]</sup>

At the end of the first year of the vertebral fracture study, there was a 49% lower risk of a new vertebral fracture in the strontium ranelate group than in the placebo group (RR 0.51; 95% CI 0.36, 0.74), and a 52% lower risk of symptomatic fracture (RR 0.48; 95% CI 0.29, 0.80). Over the entire 3-year study period, the strontium ranelate group had a 41% lower risk of a new vertebral fracture than the placebo group (RR 0.59; 95% CI 0.48, 0.73). The proportion of patients with more than one new vertebral fracture over the 3-year period was 6.4% in the strontium ranelate group and 9.8% in the placebo group (RR 0.64; 95% CI 0.44, 0.93). There was a 38% lower risk of symptomatic vertebral fracture in the strontium ranelate group than in the control group over a period of 3 years (RR 0.62; 95% CI 0.47, 0.83;  $p < 0.001$ ).<sup>[58]</sup>

Strontium ranelate was well tolerated, without any specific adverse events, and no deleterious effects on the rates of non-vertebral fractures were observed.<sup>[58]</sup>

In the whole population of the non-vertebral fracture study, strontium ranelate was associated with a 16% risk reduction for all non-vertebral fractures over a 3-year follow-up period (RR 0.84; 95% CI 0.70, 0.99) and with a 19% reduction in the risk of major non-vertebral osteoporotic fractures (RR 0.81; 95% CI 0.66, 0.98). In the high-risk fracture subgroup (women aged  $\geq 74$  years and with femoral-neck BMD T-scores less than or equal to  $-3$ ), treatment was associated with a 36% reduction in the risk of hip fracture (RR 0.64; 95% CI 0.41, 0.99). A reduction in the risk for new vertebral fracture of 39% over 3 years was obtained in the strontium ranelate group (RR 0.61; 95% CI 0.51, 0.73) with a 45% reduction (RR 0.55; 95% CI 0.39, 0.77) over the first year of treatment. In these 3640 patients, 66.4% had no prevalent vertebral fracture at inclusion. In the subgroup of patients with at least one prevalent fracture ( $n = 1224$ ; 587 in the strontium ranelate group and 637 in the placebo group), the risk of experiencing a new vertebral fracture was reduced by 32% (RR 0.68; 95% CI 0.53, 0.85).<sup>[57]</sup>

Treatment was well tolerated; the incidence of adverse events was well balanced between the two groups (87.9% in the strontium ranelate group and 88.9% in the placebo group), as was the occurrence of serious adverse events (24.7% in the strontium

ranelate group and 24.4% in the placebo group) and withdrawals due to adverse events (24.2% in the strontium ranelate group and 21.6% in the placebo group).<sup>[57,58]</sup> Nausea (7.2% vs 4.4%), diarrhea (6.7% vs 5%), headache (3.4% vs 2.4%), and dermatitis and eczema (5.5% vs 4.1%) were reported more commonly in the strontium ranelate group, but only during the first 3 months of treatment; after 3 months there was no difference between groups concerning nausea and diarrhea. Upper gastrointestinal symptoms were comparable between the two groups (incidence of gastritis: 2.3% in the strontium ranelate groups and 2.7% in the placebo group).<sup>[57]</sup>

## 8. Conclusion

Several chemical entities have shown their ability to significantly reduce both vertebral and all non-vertebral and/or hip fractures in women with established osteoporosis. Inhibitors of bone resorption (selective estrogen receptor modulators, bisphosphonates, calcitonin), anabolic agents (teriparatide), or agents with a dual mode of action (strontium ranelate) should be combined with an adequate supplementation of calcium and vitamin D.

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