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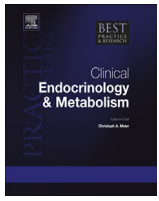

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Efficacy and safety of currently marketed anti-osteoporosis medications

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During the past 2 decades, many interventions were proven effective in the management of postmenopausal osteoporosis. The objective of an anti-osteoporosis treatment is to reduce fracture rates, ideally at all skeletal sites (i.e. spine, hip, and other non-spine). The armamentarium against osteoporosis includes anti-resorptive agents (i.e. bisphosphonates, selective estrogen receptor modulators and denosumab), bone-forming agents (i.e. peptides from the parathyroid hormone family) and one agent with a dual mechanism of action (i.e. strontium ranelate). All these medications combine antifracture efficacy with a reasonable benefit/risk profile. However, the choice of a particular chemical entity, in one individual patient is based on the knowledge and expertise of the physician. Prioritization of drugs should be based on the individual profile of the patient, the severity of osteoporosis

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and the specific contraindications, warnings and precautions of use of the various available medications.

Introduction

Osteoporosis (OP) is a common disease with an increasing prevalence, in both men and women, due to longer life expectancy [1,2]. Long-term antifracture efficacy and safety are the two major goals of any antiosteoporotic treatment [3]. Fractures (Fx) can be prevented by drugs that have different, and often opposite, effects on bone remodeling [4]. The anti-resorptive treatments decrease bone turnover and include the selective estrogen receptor modulators (SERMs), the bisphosphonates (BP) and the human monoclonal antibody to the Receptor Activator of Nuclear factor Kappa B ligand (RANKL) (denosumab (DMab)). The anabolic agents (full length [1–84] parathyroid hormone [PTH] and the 1–34 N-terminal fragment [teriparatide (TPD)]) increase bone turnover, but preferentially affect bone formation over bone resorption. Strontium ranelate (SR) is a compound with a dual mechanism of action, both stimulating formation of new bone tissue and decreasing bone resorption [5].

When treating chronic conditions associated with significant morbidity or mortality, achieving a balance between efficacy and long-term safety is essential for a successful therapy [3,6,7].

Selective estrogen receptor medulators (SERMs)

SERMs are non-hormonal compounds that have the property of binding to estrogen receptors in various tissues [7]. 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 agonistic action, or not, on other female sexual organs, such as the uterus [8].

Raloxifene (RLX) at a dose of 60 mg/day or 120 mg/day versus placebo (calcium 700 mg and vitamin D 400 IU) was first administered to postmenopausal women with a least one prevalent vertebral Fx in a study of 1-year duration [9]. Biochemical markers of bone remodeling, (BTM) such as bone-specific alkaline phosphatases (BALP) (−30% to −36%), osteocalcin (OC) (−28% to −31%) and urinary C telopeptide of type I collagen (CTx) (−31% to −39%) decreased significantly as compared with baseline values. A significant increase in the total hip bone mineral density (BMD) and the 1/3 distal radius BMD was observed as compared with baseline. A non-significant trend towards increase over controls was observed in lumbar BMD, total body and total hip BMD [9].

In the MORE study (Multiple Outcomes of Raloxifene Evaluation), 7.705 postmenopausal women (at least 2 years postmenopausal) received 60 mg or 120 mg RLX/day or placebo (PBO). All women were on calcium (500 mg/day) and vitamin D (400 IU/day) supplementation [10]. The main endpoint of MORE was the reduction of the percentage of women developing a new vertebral Fx when on RLX. Secondary endpoints were: assessing the relative risk of non-vertebral fracture, of breast cancer and of cardiovascular events. After the 3-year period, by studying the spine radiographs obtained in 6.828 women, 503 (7.4%) had at least one incident of vertebral Fx (10.1% of women in the PBO group, 6.6% of women in the 60 mg RLX group and 5.4% in those on 120 mg RLX). The relative risk (RR) of incidence of vertebral Fx was significantly decreased in both groups on RLX [RR, 0.7; 95% confidence interval (CI), 0.5–0.8 and RR, 0.5; 95% CI, 0.4–0.7) in the 60 mg and 120 mg RLX groups, respectively]. RLX at a dose of 60 mg/day reduced the risk of incident clinical vertebral Fx during the first year of therapy by 68% (RR, 0.32; 95% CI, 0.13–0.80) in the overall study population, and by 66% (RR, 0.34; 95% CI, 0.11–0.77) in the group of women with prevalent vertebral Fx. The corresponding decrease in Fx risk for the whole group was −46% (RR, 0.54; 95% CI, 0.34–0.86) after 2 years and −41% (RR, 0.59; 95% CI, 0.41–083) after 3 years [11]. The risk of non-vertebral Fx was not significantly different in the whole group of patients treated either by RLX 60 mg/day, 120 mg/day or by PBO (RR, 0.9; 95% CI, 0.8–1.1). However, in a post-hoc analysis, a subgroup of patients with a severe vertebral Fx before starting the study ($n = 614$) showed a significant risk of non-vertebral Fx within the 3 years of the study. In this group with severe OP, RLX 60 mg/day allowed a reduction of 26% of the RR of new vertebral Fx (RR, 0.74; 95% CI,

0.54–0.99) and of 47% of the non-vertebral Fx risk (clavicle, humerus, wrist, pelvis, hip and leg) (RR, 0.53; 95% CI, 0.29–0.99) [12]. During the 3 years of the MORE study, RLX led to a significant decrease (by 61%) in the incidence of one new moderate and severe vertebral Fx (RR, 0.39; 95% CI, 0.17–0.69) in women without any prevalent vertebral Fx, and by 37% (RR, 0.63; 95% CI, 0.49–0.83) in women with at least one prevalent vertebral Fx before initiation of therapy [13]. RLX (60 mg/day) was also able to significantly decrease the risk of new vertebral Fx in women without prevalent vertebral Fx, but with a lumbar BMD lower than −2.5 *T*-scores, both in women with a femoral neck BMD between −1 and −2.5 *T*-scores to start with (so-called osteopenia (RR, 0.53; 95% CI, 0.32–0.88) and in women with a lower femoral neck BMD (*T*-score < −2.5) (RR, 0.31; 95% CI, 0.06–0.71) [14]. Moreover, the extension of the MORE study to a fourth year confirmed the persistence of the anti-Fx efficacy of RLX 60 mg/day. During the fourth year, if the latter is considered separately, the risk of new vertebral Fx was reduced by 48% (RR, 0.52; 95% CI, 0.35–0.78) or by 35% (RR, 0.65; 95% CI, 0.52–0.81), according to the presence or non-presence of prevalent vertebral Fx before starting the study [15].

Some extraskeletal effects have been observed with RLX. After 3 years of therapy, 13 cases of breast cancer developed in the 5129 women on RLX versus 27 in the 2.756 women on PBO (RR, 0.24; 95% CI, 0.13–0.44). RLX reduced the risk of estrogen-receptor-positive breast cancer by 90% (RR, 0.10; 95% CI, 0.04–0.24), but not estrogen-receptor-negative invasive breast cancer (RR, 0.88; 95% CI, 0.26–3.0) [16]. In the MORE study, there was no significant difference in the incidence of combined coronary and cerebrovascular complications in the overall cohort ($n = 96$ (3.7%) in the PBO group; 82 (3.2%)) in the 60 mg/day RLX group and 94 (3.7%) in the 120 mg/day RLX group. However, in 1035 women with increased cardiovascular risk at baseline, a decrease of 40% of the risk of cardiovascular complications was observed on RLX (RR, 0.60; 95% CI, 0.38–095) [17]. Hot flashes were the most frequent side effect, leading to withdrawal from therapy in 0.1%, 0.7% and 0.5% of women on PBO, RLX 60 mg and RLX 120 mg, respectively. Leg cramps were more frequent on RLX (7% in the 60 mg group and 6.9% in the 120 mg group) versus 3.7% in the PBO group. After 3 years, RLX increased the 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) [10].

The Continuing Outcomes Relevant to Evista (CORE) trial was planned as a 3-year extension of the Multiple Outcomes of RLX Evaluation (MORE) trial in a double-blind mode [18,19]. This study was started on average 10.6 months after the end of the MORE study, because the code could evidently not be broken immediately at the end of the MORE study. Four thousand and eleven women could resume the very same treatment assigned at the start of MORE in a double-blind manner with the exception that only the 60-mg dose of RLX was compared with placebo. The patients initially assigned to the 120-mg dose in MORE continued on 60 mg in CORE. The primary objective of CORE was to evaluate the risk of breast cancer [18], with peripheral, but not the vertebral Fx, recorded as adverse effects. Furthermore, other treatments aimed at improving bone status were allowed, BP therapy being more frequent in the former RLX group than in the PBO group. Only 386 women took no bone-acting drug during 8 years, and 259 were on RLX. The latter ones maintained their BMD values both at the spine and at the hip [19]. After 8 years (4 years in MORE, 3 years in CORE, plus nearly 1 year in between without SERM therapy), RLX therapy led to BMDs higher by 2.2% at the spine and by 3% at the total hip, comparatively with PBO. There was no statistically significant difference in the incidence of non-vertebral Fx between both groups [19]. In a post-hoc analysis, the risk of new non-vertebral Fx at six skeletal sites (clavicle, humerus, wrist, pelvis, hip and lower leg) was statistically significantly decreased in CORE patients suffering from prevalent vertebral Fx at MORE baseline and in women with semi quantitative grade 3 vertebral Fx in the combined MORE and CORE trials on RLX [19]. It is interesting to note that during the time interval between the end of MORE and the start of CORE (on average 337 ± 85 (SD) days), a significant bone loss was observed at the spine and the femoral neck in the RLX group, correlated at the spine with the length of time off of study drug. Moreover, in another study, treatment discontinuation for 1 year after 5 years of continuous therapy with RLX was also accompanied with significant BMD declines both at the lumbar spine (−2.4 ± 2.4%) and the hip (−3.0 ± 3.0%), an effect comparable with estrogen weaning [20]. There is no data available, however, on Fx incidence following RLX discontinuation [20].

At the end of the 8-year study period of MORE + CORE, the reduction in invasive breast cancer amounted to 66% (RR, 0.34; 95% CI, 0.22–0.50) and in invasive estrogen-receptor-positive breast cancers

to 76% as compared with PBO (RR, 0.24; 95% CI, 0.15–0.40) [18]. In contrast, there was no statistically significant difference in the incidence of invasive estrogen-receptor-negative breast cancer between groups. Regardless of invasiveness, the overall incidence of breast cancer decreased by 58% in the RLX group (RR, 0.42; 95% CI, 0.29–0.60) compared with the placebo group. Endometrial tolerance (hyperplasia, cancer, or vaginal bleedings) was not different from placebo [18]. A non-significant increase in the risk of deep venous thrombosis persisted in the CORE study (RR, 2.17; 95% CI, 0.83–5.70) [18].

In another study versus PBO, concerning 10.101 post-menopausal women (mean age, 67.5 years) with coronary heart disease or multiple risk factors for coronary heart disease, RLX (60 mg/day) did not modify significantly the risk of primary coronary events but confirmed a reduction in the risk of invasive breast cancer (RR, 0.56; 95% CI, 038–0.83) [21]. The risk of clinical vertebral Fx (RR, 0.65; 95% CI, 0.47–0.89) was also reduced. However, RLX therapy was associated with an increased risk of fatal stroke (RR, 1.49; 95% CI, 1.0–2.24) and venous thromboembolism (RR, 1.44; 95% CI, 1.06–1.95). In the STAR study involving 19.647 postmenopausal women with increased 5-year breast cancer risk, RLX was shown to be as effective as tamoxifen in reducing the risk of invasive breast cancer [22]. In this study, RLX demonstrated a lower risk of thromboembolic events and cataracts, but a non-significant higher risk of non-invasive breast cancer as compared with tamoxifen [22].

Bazedoxifene (BZA) has been approved in Europe and Japan for the treatment of OP in post-menopausal women at an increased risk of Fx [23].

A pivotal, 3-year OP treatment study ($N = 7492$) evaluated the efficacy and safety of BZA in post-menopausal women (aged 55–85 years) with OP, as defined by low BMD or radiographically confirmed vertebral Fx [24–26].

Subjects were randomized to daily oral treatment with BZA 20 or 40 mg, RLX 60 mg, or PBO and also received daily calcium and vitamin D. The primary endpoint of the 3-year core study was the incidence of new vertebral Fx; secondary endpoints included the incidence of clinical vertebral Fx and non-vertebral Fx and changes from baseline in BMD and BTMs.

At 3 years, BZA 20 and 40 mg significantly reduced the incidence of new vertebral Fx compared with PBO (Kaplan–Meier estimates of 2.3%, 2.5%, and 4.1%, respectively; $p < 0.05$ for both BZA doses versus PBO) [26]. The risk of new vertebral Fx was reduced by 42% and 37% with BZA 20 and 40 mg, respectively; corresponding hazard ratios (HRs) and 95% CI were 0.58 (0.38–0.89)with BZA 20 mg and 0.63 (0.42–0.96) with BZA 40 mg compared with PBO. There were no significant differences between the BZA and RLX groups in the incidence of new vertebral Fx at 3 years.

At 3 years, no difference in the incidence of non-vertebral Fx was observed for BZA compared with PBO in the overall study population [26]. However, a post-hoc analysis in a subgroup of women at a higher risk of Fx (femoral neck BMD *T*-score of −3 and/or 1 moderate or severe vertebral Fx or multiple mild vertebral fractures at baseline; $n = 1772$) showed a significant reduction of 50% (HR, 0.50; 95% CI, 0.28–0.90) in the risk of non-vertebral Fx for BZA 20 mg compared with PBO ($p = 0.02$). In these women, BZA 20 mg also significantly reduced the risk of non-vertebral Fx by 44% (HR, 0.56; 95% CI, 0.31–1.01) compared with RLX 60 mg ($p = 0.05$). A slight reduction in the risk of non-vertebral Fx observed with BZA 40 mg (HR, 0.70; 95% CI, 0.40–1.20) did not reach statistical significance [26].

Consistent with findings from the subgroup analysis, a reanalysis of study findings using FRAX showed that BZA (combined data for the 20- and 40-mg groups) significantly reduced the risk of non-vertebral Fx compared with PBO in women with 10-year Fx probabilities $\geq$16%, as assessed by FRAX, with greater treatment effect observed with increasing Fx probability [27]. In another similar reanalysis, significant reductions in the risk of non-vertebral Fx compared with PBO were observed in women with 10-year Fx probabilities >20% for BZA 20 mg, BZA 40 mg, and BZA 20 and 40 mg combined (HR, 0.449, 0.438, and 0.447, respectively; $p < 0.05$ for all BZA groups). In contrast, assessment of RLX 60 mg in this reanalysis showed no significant reduction in the risk of non-vertebral Fx in any subgroup compared with PBO [28,29].

At 5 years in the BZA treatment study, incidences of non-vertebral Fx in the overall study population were similar among the BZA and PBO groups, consistent with findings at 3 years [30]. In a subgroup analysis of subjects at a higher risk of Fx at 5 years ($n = 1324$), BZA 20 and 40/20 mg showed reductions of 37% (HR, 0.63; 95% CI, 0.38–1.03) and 31% (HR, 0.69; 95% CI, 0.42–1.13), respectively, in the risk of non-vertebral Fx compared with PBO that did not reach statistical significance. However, combined data from the BZA 20- and BZA 40/20-mg groups at 5 years showed a significant reduction of 34% (HR, 0.66; 95% CI, 0.44–0.995) in non-vertebral Fx risk compared with PBO ($P = 0.049$) [34].

Overall, BZA was associated with a favorable endometrial and breast safety profile in the 3-year osteoporosis treatment study [25]. BZA did not increase endometrial thickness or the incidences of endometrial hyperplasia and carcinoma compared with PBO [25]. The incidences of breast carcinoma, cysts, and pain were low and similar between groups. There was a lower incidence of fibrocystic breast disease with BZA 20 or 40 mg compared with PBO or RLX 60 mg (0.3% for BZA 20 mg, 0.2% for BZA 40 mg, 0.5% for PBO, and 0.8% for RLX 60 mg; overall $p = 0.038$) [31,32]. A retrospective, ancillary study showed that changes in mammographic breast density at 2 years with BZA 20 and 40 mg were not significantly different from those with PBO or RLX 60 mg [33].

Results from the two 2-year extensions (Extension I and II) showed that BZA was associated with a favorable endometrial and breast safety profile over 7 years of treatment [31,32]. Incidences of endometrial, breast-related, and other reproductive tract AEs were generally low and evenly distributed between groups at 5 and 7 years, similar to that observed at 3 years. At 7 years, there were fewer reports of endometrial carcinoma in the BZA 20 mg ($n = 0$) and BZA-treated groups ($n = 3$) than in the PBO group ($n = 7$; $p < 0.05$ for both). There were numerically more cases of ovarian carcinoma with the BZA 20-mg ($n = 3$) and BZA-treated ($n = 4$) groups over 7 years of treatment compared with PBO ($n = 0$), but these differences were not statistically significant [31,35,36].

Bisphosphonates

Alendronate (ALN), risedronate (RIS), ibandronate (IBN) and zoledronic acid (ZA) are currently registered for the treatment of osteoporosis. BP may be associated with gastrointestinal complaints, and therapeutic schemes for oral BP are mandatory constraining. Inconvenience and complexity of required dosing procedures with oral BP therapy are factors that hinder medication persistence leading to suboptimal health care outcomes. These are reasons why alternative approaches have been developed. Repeated infusions of potent BP at large time intervals were expected to circumvent these constraints.

The antifracture efficacy of ALN has been established in large populations of postmenopausal women [37–39]. In a study including 2027 women with prevalent vertebral Fx at baseline, ALN reduced the incidence of new vertebral Fx by 47% (RR, 0.53; 95% CI, 0.41–068) [38]. The incidence of vertebral Fx 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 Fx (RR, 0.80; 95% CI, 0.63–1.01), but hip Fx incidence was also reduced (RR, 0.49; 95% CI, 0.23–0.99) as was wrist Fx risk (RR, 0.52; 95% CI, 0.31–0.87) [38]. Estimation of the effect on hip Fx was not precise and the CI correspondingly wide, reflecting that the number of Fx (33 in total) was small. The antifracture efficacy of ALN was also demonstrated in 4.432 women with low bone mass but without vertebral Fx at baseline treated for 4 years (5 mg daily during the first 2 years, then 10 mg daily). The reduction in the incidence of radiological vertebral Fx was 44% (RR, 0.56; 95% CI, 0.39–0.80). However, the reduction in clinical Fx was not statistically significant in the whole group but well among women with initial *T*-scores below −2.5 at the femoral neck (RR, 0.64; 95% CI, 0.50–0.82). No reduction was observed in the risk of non-vertebral Fx (RR, 0.88; 95% CI, 0.74–1.04) [39].

The effect of ALN on non-vertebral Fx has been estimated in a meta-analysis of five PBO-controlled trials of at least 2 years duration including postmenopausal women with a *T*-score < -2.0. The estimated cumulative incidence of non-vertebral Fx after 3 years was 12.6% in the PBO group and 9.0% in the ALN group (RR, 0.71; 95% CI, 0.502–0.997) [40]. Another meta-analysis estimated that ALN reduced vertebral Fx incidence by 48% when given at 5 mg daily or more (RR, 0.52; 95% Ci, 0.43–0.65) and non-vertebral Fx rate by 49% when given at 10 mg daily or more (RR, 0.51; 95% CI, 0.38–0.69) [41]. However, data from one of the largest trials with ALN [42] were excluded from this meta-analysis [41]. Data have been reported from patients discontinuing ALN treatment after 5 years or continuing for 10 years [42,43]. There was no evidence that discontinuation of ALN for up to 5 years increases Fx risk [42].

ALN was well tolerated in these different PBO-controlled trials, but patients at risk for upper gastrointestinal events were excluded from the trials, and subsequent experience has undoubtedly demonstrated that esophageal and, to a lesser extent, gastric toxicity can be troublesome adverse events, especially if proper intake instructions are not respected. Several cases of esophageal ulcerations have thus been described [44].

Daily compliance with 10 mg ALN is uncertain and difficult to maintain in routine clinical practice. The efficacy and safety of treatment with oral once-weekly ALN 70 mg, twice-weekly ALN 35 mg, and daily ALN 10 mg have been compared in a double-blind, 1-year study involving a total of 1258 postmenopausal osteoporotic women. The increases in BMD at the lumbar spine, hip, and total body were similar for the three dosing regimens, and the fall in BTM was also quite similar. The gastrointestinal tolerance of the once-weekly regimen and the daily dosing were similar. The antifracture efficacy of the weekly formulation is supposed to be similar to the daily formulation, but this has not been formally tested [45].

Generic ALN sodium tablets are now available with a theoretical bioequivalence to the branded product. Differences in in vitro disintegration and esophageal transit with generic formulations of alendronic acid 70-mg tablets have been reported [46]. Some concern remains for the clinician that the pharmaceutical properties of the various generic formulations may affect the potential for esophageal irritation and tolerability, the bioavailability, and the potency of generic ALN. The question of lower bioavailability or potency of generic ALN remains open [47].

RIS at the dose of 5 mg daily for 3 years has been shown to significantly reduce the vertebral Fx risk in established OP as compared with PBO. In women with at least one vertebral Fx at baseline, the relative reduction of new vertebral Fx was 41% (RR, 0.59; 95% CI, 0.42–0.82) and 39% for non-vertebral Fx (RR, 0.61; 95% CI, 0.39–0.94) [48]. In women with at least two vertebral Fx at baseline, the risk of new vertebral Fx was reduced by 49% (RR, 0.51; 95% CI, 0.36–0.73) but, in this study, the effect on new non-vertebral Fx was not significant (RR, 0.67; 95% CI, 0.44–1.04) [49]. The European study [61] was continued blindly in a subset of the population, and the antifracture efficacy was maintained for at least 5 years [50]. Vertebral Fx risk reduction with RIS was confirmed in women over 80 with documented OP (RR, 0.56; 95% CI, 0.39–081) [51].

RIS has also been shown to decrease the incidence of hip Fx in a controlled trial specifically designed for that purpose. Hip Fx reduction was only observed in women with documented OP, however. In this PBO-controlled study involving 5.445 women 70–79 years old who had OP and/or risk factors for falls, it was shown that RIS at 2.5 or 5 mg/day for 3 years (the actual mean duration of treatment was 2 years) lowered the RR of hip Fx by 40% (RR, 0.60; 95% CI, 0.40–0.90). There was no dose effect and, interestingly, the effect was greater in the group of women who had a vertebral Fx at baseline (RR, 040; 95% CI, 0.20–0.80). In the same study, however, there was no significant effect of RIS in 3886 women $\geq$80 years old (RR, 0.80; 95% CI, 0.60–1.20). Like ALN, RIS also had a safe profile in clinical trials. The safety profile of RIS was similar to that of PBO, despite the fact that unlike in the ALN trials, patients with a history of gastrointestinal disease or chronic use of non-steroidal anti-inflammatory drugs were not excluded from the RIS studies. A weekly formulation of RIS 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 (BMD) and on bone turnover (BTM) [52].

The iBandronate Osteoporosis trial in North America and Europe (BONE) has been the first study to prospectively demonstrate a reduction of vertebral Fx risk of an intermittent BP regimen [53]. A 2.5-mg daily oral IBN and an intermittent oral IBN dosage (20 mg every other day for 12 doses every 3 months) were assessed in a 3-year PBO-controlled trial including 2946 osteoporotic women with prevalent vertebral Fx. The RR reductions of new morphometric vertebral Fx, compared with PBO, were 62% (RR, 0.38; 95% CI, 0.25–0.59) and 50% (RR, 0.50; 95% CI, 0.34–0.74) for the daily and intermittent groups, respectively. The incidence on non-vertebral Fx was similar between the IBN and PBO groups after 3 years (9.1%, 8.9% and 8.2% in the daily, intermittent, and PBO groups, respectively). The overall population was at low risk for osteoporotic Fx (mean total hip BMD *T*-score, −1.7), but post-hoc analysis, in higher-risk subgroups, showed that the daily regimen reduced the risk of non-vertebral Fx (femoral neck BMD *T*-score < -3.0, 69%; $p = 0.012$); (lumbar spine BMD *T*-score < -2.5 and history of a clinical Fx, 62%; $p = 0.025$).

The oral 150-mg dose of monthly IBN has been evaluated in the Monthly Oral IBN in Ladies (MOBILE), a 2-year, multicenter, double-blind, non-inferiority bridging study comparing the efficacy and safety of once-monthly IBN with daily IBN in 1609 postmenopausal women [54]. The 150-mg once-monthly dose of IBN consistently produced greater sCTX suppression and greater increase in lumbar and total hip BMD ($p < 0.05$) than the daily regimen, but the cumulative dose was larger. Once-monthly IBN was as well tolerated as daily treatment. These results were confirmed in the MOBILE 3-year extension study [55].

The Dosing Intravenous Administration trial (DIVA) is a randomized, double-blind, double dummy, non-inferiority, international multicenter trial comparing daily 2.5 mg oral IBN and intermittent intravenous IBN, given 2 mg every 2 months or 3 mg every 3 months, in 1395 postmenopausal women [56]. All patients had OP (lumbar spine *T*-score < -2.5). The primary endpoint was change from baseline in lumbar spine BMD at 1 year. At 1 year, mean lumbar spine BMD increases were 5.1%, 4.8%, and 3.8% in the intravenous 2 mg, the intravenous 3 mg, and the oral daily 2.5 mg groups, respectively. Both of the intravenous regimens not only were non-inferior but also were superior ($p < 0.001$) to the oral regimen. Hip BMD increases were also significantly greater in both intravenous groups.

The IBN dose response for the prevention of non-vertebral Fx has been evaluated in a pooled analysis of individual patient data from eight randomized trials [57]. This study was conducted to assess the effect of high versus lower doses of IBN on non-vertebral Fx based on annual cumulative exposure (ACE). ACE was defined as the total annual dose of BP absorbed and therefore available to the bone tissue taking into account the fact that 100% of an intravenous BP and 0.6% of an oral dose are absorbed. The results were adjusted for clinical Fx, age, and BMD. High ACE dose defined as $\geq$10.8 mg (150 mg once monthly, 3 mg i.v. every 3 months, and 2 mg i.v. every 2 months) were compared to ACE doses $\leq$7.2 mg (100 mg oral monthly, 50/50 mg monthly, and 2.5 mg oral daily) and to low 5.5 mg ACE dose (oral 2.5 mg daily). A non-response effect on non-vertebral Fx was observed when comparing high with low ACE doses. The comparison resulted in a 0.62 RR (95% CI, 0.396–0.974; $p = 0.038$) for ACE doses $\geq$ 10.8 mg versus 5.5 mg ACE doses and in a 0.64 RR (95% CI, 0.43–0.94) for $\geq$10.8 mg ACE doses versus $\leq$7.2 mg ACE doses, leading to the conclusion that higher IBN dose levels (150 mg monthly or 3 mg i.v. quarterly) significantly reduced non-vertebral Fx risk in postmenopausal women.

A similar analysis compared reduction in Fx risk for high ($\geq$10.8 mg), mid (7.2–5.5 mg), and low ($\leq$4.0 mg) ACE relative to PBO. It was observed that doses of IBN resulting in ACEs $\geq$10.8 mg, including the marketed oral 150 mg monthly and i.v. 3 mg thrice monthly, significantly reduce the risk of all clinical, vertebral, and non-vertebral Fx with a 0.71 RR (95% CI, 0.55–0.92; $p = 0.01$). The risk of non-vertebral Fx was also significantly reduced with a 0.70 RR (95% CI, 0.50–0.99; $p = 0.04$). Data from the four phase III clinical trials of IBN (8710 patients) were pooled in a meta-analysis to assess the relationship between IBN dose, BMD changes, and rates of both clinical and non-vertebral Fx. It was observed that both lumbar spine and total hip BMD increased with increasing IBN dose. A statistically significant inverse linear relationship has been reported between percent change in lumbar spine BMD and the rate of clinical Fx ($p = 0.005$) [58].

There is no evidence, from PBO-controlled trials, for a reduction of non-vertebral Fx with IBN, but data from the MOBILE bridging study, from meta-analysis and from ACE evaluations, suggest a significant effect of the marketed oral 150 and the 3 mg i.v. IBN on the risk reduction of non-vertebral Fx. Hip, non-vertebral, or clinical Fx rates were not statistically different between patients receiving monthly oral IBN, weekly oral ALN, or RIS in a 12-month observational study, but patients on oral IBN had a significantly 64% lower risk of vertebral Fx than patients on weekly BP (RR, 0.36; 95% CI, 0.18–0.75; $p = 0.006$) [59].

More recently a pooled analysis of DIVA and MOBILE long-term extension studies showed that for IBN regimens with ACE $\geq$10.8 mg, given for 5 years, time to Fx was significantly longer for all clinical Fx, non-vertebral Fx and clinical Fx versus placebo ($p = 0.005$) [60].

Both oral 2.5 mg daily and intermittent oral IBN dosage (20 mg every other day for 12 doses every 3 months) were well tolerated with an incidence of adverse events similar to PBO in the BONE trials [53]. Once-monthly oral IBN was well tolerated, with a similar safety profile to placebo in a 3-months, double-blind, placebo-controlled, phase 1 study (Monthly Oral Pilot Study) [61] and with a similar incidence of adverse events across groups (oral 50 + 50, 100, and 150 mg) in the MOBILE study [54]. The incidence of upper gastrointestinal adverse events was similar for the once-weekly 70-mg ALN and the once-monthly 150-mg IBN in a 12-month comparative study [62]. After 1 year, the incidence of proportion of patients with any adverse events, treatment-related adverse events, and treatment-related adverse events that led to withdrawal was similar for the i.v. 2-mg twice monthly, 3-mg thrice monthly, and oral 2.5-mg ibandronate in the DIVA trial [56].

ZA is the latest of the aminobisphosphonates available for parenteral osteoporosis treatment. It has the highest affinity among BP for bone surfaces, the maximum inhibition potency to inhibit the activity of the farnesyl diphosphate synthesis, and the highest anti-resorptive activity. In the Health Outcome

and Reduced Incidence with Zoledronic Acid Once Yearly Pivotal Fracture Trial (HORIZON PFT), a yearly infusion of ZA (5 mg over 15 min) given at 0, 12 and 24 months was compared to a PBO infusion in more than 7500 postmenopausal women with OP who were followed up for 3 years. All patients received daily calcium and vitamin D supplements (1000–1500 mg/400–1200 IU). The BTM were decreased by 30%–59% at 12 months. BMD increased significantly ($p < 0.001$) at the femoral neck (5.06%; 95% CI, 4.76–6.28), total hip (6.02%; 95% CI, 5.77–6.28) and lumbar spine (6.71%; 95% CI, 5.69–7.74). The 3-year risk of morphometric vertebral Fx was reduced by 70% (RR, 0–30; 95% CI, 0.24–0.38) and that of hip Fx by 41% (RR, 0.59; 95% CI, 0.42–0.83). Non-vertebral Fx were decreased by 25% (RR, 0.75; 95% CI, 0.64–0.87). Clinical vertebral Fx were reduced by 77% (RR, 0.23; 95% CI, 0.14–0.37) and all clinical Fx were reduced by 33% (RR, 0.67; 95% CI, 0.58–0.77; $p < 0.001$) [63].

In a second study including more than 2100 patients (HORIZON Recurrent Fx Trial), men and women over 50 years old received ZA or a PBO infusion within 90 days after repair of a hip Fx. In this only trial conducted to study the risk of Fx in patients with a prevalent hip Fx, not only was the risk of a new clinical Fx reduced by 35% (RR, 0.65; 95% CI, 0.50–0.84; $p < 0.001$) in the ZA group during the 1.9 years follow-up but the risk of death was also reduced by 28% (RR, 0.72; 95% CI, 0.56–0.93) in this arm [64]. A significant reduction of Fx risk was already observed at 12 months. The decreased mortality is only partly explained by the reduction of Fx rates [65].

In these two controlled studies, the profile was safe, with a number of serious adverse events or deaths not significantly different in the groups treated with ZA or with PBO. A major problem with ZA was the postinfusion syndrome, which is classical with all intravenous BP following the first infusion, usually mild, and can be reduced by acetaminophen [66]. Intriguingly, an unexpected number of episodes of atrial fibrillation described as severe adverse events occurred in the ZA-treated group. The fact that the total incidence of atrial fibrillation was not increased, that the episodes occurred late after the injection, and that an increased frequency of AF was not found in the HORIZON-RFT trial suggests that this occurred by chance [67]. A recent meta-analysis provided no evidence for an excess risk of atrial fibrillation in patients treated with BP [67]. This study did not reveal any increase in the risk of stroke or cardiovascular mortality. Asymptomatic hypocalcaemia occurred in a few patients treated with ZA, most frequently 9–11 days after the infusion. Serum creatinine increased transiently in some patients of the ZA group. However, in the long-term, there was no alteration of the renal function [68].

HORIZON PFT was extended to 6 years, with 1233 women who received ZA for 3 years in the core study were randomized to 3 additional years of ZA or PBO. New morphometric vertebral Fx were lower in ZA whereas other Fx were not different suggesting that many patients may discontinue therapy up to 3 years while those at high risk of vertebral Fx may benefit from continued treatment [69].

In a post-hoc analysis of the HORIZON PFT based on postrandomization subgroup, Fx risk appears to be reduced for more than 1 year after a single infusion of ZA, suggesting that an optimal benefit/risk ratio of ZA could be obtained by a single infusion [70].

Adherence to treatment is crucial to reach high-level efficiency and low level of side effects. In clinical practice, adherence is poor in osteoporotic patients. It has been measured that approximately 75% of women who initiate OP drug therapy are non-adherent within 12 months, almost 50% having discontinued their therapy by this time. This is not only observed in asymptomatic osteoporotic patients but also after such a severe event as a hip Fx. Prescription rate and compliance with BP or SERMs after hip Fx have been measured in 23,146 patients who had sustained a hip Fx. Of these patients, 6% received treatment during the study period (4.6% ALN, 0.7% RIS, and 0.7% RLX). At 12 months, the rate of persistence was 41%, and the median duration of persistence was 40.3 weeks [71]. An important factor is the frequency of drug administration. Medication persistence has been compared for patients receiving weekly oral or daily oral BP in a large, longitudinal cohort of female patients ($n = 211{,}319$) receiving prescriptions for ALN or RIS from approximately 14,000 US retail pharmacies. Only 56.7% of patients receiving the weekly regimen and only 39.0% of patients receiving the daily regimen continued to take BP therapy at month 12 of the study period ($p < 0.0001$) [72].

A recent network meta-analysis comparing BP gastrointestinal safety found that ZA had the highest probability of having the highest number of any gastrointestinal adverse event (91%) and nausea (70%). These results strongly question the assumption that annual ZA will translate into better adherence than oral BP [73].

The second report of a task force of the American Society for Bone and Mineral Research concluded that although the RR of patients with atypical femoral fractures and BP use is high, the absolute risk of atypical femoral Fx in patients on BP is low, ranging from 3.2 to 50 cases per 100.000 person-years. However, long-term use may be associated with higher risk (±100 per 100.000 person-years). When BP are stopped, risk of atypical femoral fractures may decline [74].

Overall, long-term extension trials with the BP show that these agents are well tolerated, with no new safety concerns compared with safety data gathered during the first 3 years of the pivotal studies. Nevertheless, there is growing concern that long-term suppression of bone turnover with BP may lead to micro-damage accumulation. The current hypothesis regarding the pathophysiology of atypical femoral fractures is that long-term suppression of bone turnover leads to changes in bone quality and mechanical function, which allow the progression of bone micro-damage. BP suppress the targeted repair of cracks by bone metabolic units, which eventually leads to the development of an insufficiency Fx at the point of maximal, weight-bearing stress, namely at the subtrochanteric or diaphyseal femur [75]. The Fx are regarded as 'atypical' in that they involve the strongest part of the femur, namely the subtrochanteric and diaphyseal region, and are characterized by features distinctly different from 'typical' osteoporotic femur Fx [76].

A Working Group of the European Society on Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) and the International Osteoporosis Foundation (IOF) has reviewed the evidence for a causal association between subtrochanteric Fx and long-term treatment with BP [77]. They concluded that while BP use may be associated with atypical subtrochanteric Fx, the numbers involved are so small that the risk–benefit ratio would still remain favorable for the use of BP to prevent Fx.

Delayed healing can complicate the treatment of atypical Fx [78]. However, several studies have reported healing of atypical subtrochanteric femoral Fx with TPD [79,80]. Promising results have also been achieved with SR [80,81].

Osteonecrosis of the jaw is the appearance of exposed bone in the mandible, maxilla, or both that persists for at least 8 weeks in the absence or radiotherapy or jaw metastases [82]. The condition is known to affect patients receiving IV BP for metastatic disease [83]. Patients in oncology generally receive much larger doses than those with OP. Assessment of causality is very difficult, though there is a possible role of inflammation and infection [84,85].

The association of osteonecrosis of the jaw and BP treatment for OP has already been the subject of a separate ESCEO Working Group paper [85]. Osteonecrosis of the jaw is very rare with oral BP in the management of OP, and current estimates of incidence stand at around 1/38,000 patient-years of treatment [85–88]. Data from the GPRD and The Health Improvement Network (THIN) suggest that the annual incidence of all osteonecrosis is 2–3/100,000, independently of BP use [89,90].

There have been no cases of osteonecrosis of the jaw reported with RIS in RCTs, and the post-approval reporting rate is <2/100,000 patient-years, with 434 reports in which 30–35% of patients had taken the drug for <1 year [90]. There were two cases of osteonecrosis of the jaw in the HORIZON trial, one in the ZA group and one in the placebo group [91]. The rate in the ZA-treated osteoporotic population is currently estimated at 0.9/100,000 patient-years of treatment. For IBN, the rate is 0.9/100,000 patients exposed in OP versus 2.3/100,000 patients exposed in oncology [92].

Denosumab (human monoclonal antibody to receptor activator for nuclear factor Kappa B ligand)

Receptor activator for nuclear factor Kappa B ligand (RANKL), a member of the Tumor Necrosis Factor (TNF) super family, is expressed by osteoblasts and their immature precursors and is necessary and sufficient for osteoclastogenesis. RANKL activates its receptor, RANK, which is expressed on osteoclasts and their precursors, thus promoting osteoclasts formation and activation and prolonging osteoclasts survival by suppressing apoptosis [93]. In vivo, the effects of RANKL are counteracted by osteoprotegerin (OPG), a soluble neutralizing decoy receptor. Elderly women with hip fractures exhibit an increased RANKL/OPG mRNA content of iliac bone [94].

DMab is a fully monoclonal antibody that works by binding RANKL and inhibiting the signaling cascade that causes osteoclast maturation activity and survival. A multi-center, double-blind study compared the efficacy and safety of DMab with ALN in postmenopausal women with low bone mass.

1189 postmenopausal women with a *T* score </ = −2.0 at the lumbar spine or total hip were randomized 1:1 to receive subcutaneous DMab injections (60 mg every 6 months) plus oral PBO weekly ($n = 594$) or oral ALN weekly (70 mg) plus subcutaneous PBO injections every 6 months ($n = 595$). Changes in BMD were assessed at the total hip, femoral neck, trochanter, lumbar spine, and 1/3 radius at 6 and 12 months, and in BTM at months 1, 3, 6, 9, and 12. Safety was evaluated by monitoring adverse events and laboratory values. At the total hip, DMab significantly increased BMD compared with ALN at month 12 (3.5% versus 2.6%; $p < 0.0001$) Furthermore, significantly greater increases in BMD were observed with DMab treatment at all measured skeletal sites (12-month treatment difference: 0.6% femoral neck; 1.0% trochanter; 1.1% lumbar spine; 0.6% 1/3 radius; $p < 0.0002$ all sites). DMab treatment led to significantly greater reduction of BTM compared with ALN therapy. Adverse events and laboratory values were similar for DMab- and ALN-treated subjects. DMab demonstrated significantly larger gains in BMD and greater reduction in BTM compared with ALN. The overall safety profile was similar for both treatments [95].

7868 women between the ages of 60 and 90 years who had a BMD *T* score of less than −2.5 but not less than −4.0 at the lumbar spine or total hip were randomly assigned to receive either 60 mg of DMab or PBO subcutaneously every 6 months for 36 months in the Fracture Reduction Evaluation of Denosumab in Osteoporosis every 6 Months (FREEDOM) study. The primary endpoint was new vertebral Fx. Secondary endpoints included non-vertebral and hip Fx [96].

As compared with PBO, DMab reduced the risk of new radiographic vertebral Fx, with a cumulative incidence of 2.3% in the DMab group, versus 7.2% in the PBO group (RR, 0.32; 95% CI, 0.26–0.41; $p < 0.001$). DMab reduced the risk of hip Fx, with a cumulative incidence of 0.7% in the DMab group, versus 1.2% in the PBO group (HR, 0.60; 95% CI, 0.37–0.97; $p = 0.04$). DMab also reduced the risk of non-vertebral Fx, with a cumulative incidence of 6.5% in the DMab group, versus 8.0% in the PBO group (HR, 0.80; 95% CI, 0.67–0.95; $p = 0.01$). There was no increase in the risk of cancer, infection, cardiovascular disease, delayed fracture healing, or hypocalcemia, and there were no cases of osteonecrosis of the jaw and no adverse reactions to the injection of DMab [96].

Participants who completed the FREEDOM trial were eligible to enter an extension to continue the evaluation of DMab efficacy and safety for up to 10 years. For the 5-year extension results, women from the FREEDOM DMab group had 2 more years of DMab treatment (long-term group) and those from the FREEDOM PBO group had 2 years of DMab exposure (cross-over group). A total of 4550 women enrolled in the extension (2343 long-term; 2207 cross-over). Reductions in BTMs were maintained (long-term group) or occurred rapidly (cross-over group) following DMab administration. In the long-term group, lumbar spine and total hip BMD increased further, resulting in 5-year gains of 13.7% and 7.0%, respectively. In the cross-over group, BMD increased at the lumbar spine (7.7%) and total hip (4.0%) during the 2-year DMab treatment. Yearly Fx incidences for both groups were below rates observed in the FREEDOM PBO group and below rates projected for a "virtual untreated twin" cohort. Adverse events did not increase with long-term DMab administration. Two adverse events in the cross-over group were adjudicated as consistent with osteonecrosis of the jaw. The authors concluded that five-year DMab treatment of women with postmenopausal OP maintained BTM reduction and increased BMD, and was associated with low Fx rates and a favorable risk/benefit profile [97].

Women from the FREEDOM DMab group received 3 more years of DMab for a total of 6 years (long-term) and women from the FREEDOM PBO group received 3 years of DMab (crossover). In the long-term group, BMD further increased for cumulative 6-year gains of 15.2% (lumbar spine) and 7.5% (total hip). During the first 3 years of DMab treatment, the crossover group had significant gains in lumbar spine (9.4%) and total hip (4.8%) BMD, similar to the long-term group during the 3-year FREEDOM trial. In the long-term group, Fx incidences remained low and below the rates projected for a virtual PBO cohort. In the crossover group, 3-year incidences of new vertebral and non-vertebral Fx were similar to those of the FREEDOM DMab group. Incidence rates of adverse events did not increase over time. Six participants had events of osteonecrosis of the jaw confirmed by adjudication. One participant had an Fx adjudicated as consistent with atypical femoral fracture. The authors concluded that DMab treatment for 6 years remained well tolerated, maintained reduced BTM, and continued to increase BMD [98].

Whereas discontinuation of DMab has been associated with transient increases in bone remodeling and declines in bone mineral density (BMD), the effect on Fx risk during treatment cessation is not as

well characterized. To understand the Fx incidence between treatment groups after cessation of investigational product, subjects in FREEDOM who discontinued treatment after receiving two to five doses of DMab or PBO, and continued study participation for ≥7 months were evaluated. The off-treatment observation period for each individual subject began 7 months after the last dose and lasted until the end of the study. This subgroup of 797 subjects (470 PBO, 327 DMab), who were evaluable during the off-treatment period, showed similar baseline characteristics for age, prevalent Fx, and lumbar spine and total hip BMD *T*-scores. During treatment, more PBO-treated subjects as compared with DMab-treated subjects sustained a Fx and had significant decreases in BMD. During the off-treatment period (median 0.8 years per subject), 42% versus 28% of PBO- and DMab-treated subjects, respectively, initiated other therapy. Following discontinuation, similar percentages of subjects in both groups sustained a new Fx (9% PBO, 7% DMab), resulting in a fracture rate per 100 subject-years of 13.5 for PBO and 9.7 for DMab (HR 0.82; 95% CI, 0.49–1.38), adjusted for age and total hip BMD *T*-score at baseline. There was no apparent difference in Fx occurrence pattern between the groups during the off-treatment period [99].

The BTM substudy of the FREEDOM trial included 160 women randomized to subcutaneous DMab (60 mg) or PBO injections every 6 months for 3 years. Biochemical markers of bone resorption (serum CTX, tartrate resistant acid phosphatases [Trap-5b], and bone formation (serum procollagen type I N-propeptide (PINP)), BALP) were measured at baseline, 1, 6, 12, 24, and 36 months. Decreases in CTX were more rapid and greater than decreases in PINP and BALP. One month post-injection, CTX levels in all DMab-treated subjects decreased to levels below the premenopausal reference interval. CTX values at the end of the dosing period were influenced by baseline CTX values and the dosing interval. The percentage of subjects with CTX below the premenopausal reference interval before each subsequent injection decreased from 79% to 51% during the study. CTX and PINP remained below the premenopausal reference interval at all-time points in 46% and 31% DMab-treated subjects, respectively. With DMab, but not PBO, there were significant correlations between CTX reduction and BMD increase (*r*-value: −0.24 to −0.44) [100].

The primary data of the phase 3 FREEDOM study of the effects of DMab in women with postmenopausal OP were used to compute country-specific probabilities using the FRAX tool (version 3.2). At baseline, the median 10-year probability of a major osteoporotic Fx (with BMD) was approximately 15% and for hip Fx, the risk was approximately 5%, in both groups. In the simplest model adjusted for age and fracture probability, treatment with DMab over 3 years was associated with a 32% (95% CI 20%–42%) decrease in clinical osteoporotic Fx. DMab reduced Fx risk to a greater extent in those at moderate to high risk. For example, at 10% probability, DMab decreased Fx risk by 11% ($p = 0.63$), whereas at 30% probability (90th percentile of study population) the reduction was 50% ($p = 0.001$). The reduction in Fx was independent of prior Fx, parental history of hip Fx, or secondary causes of OP. A low body mass index (BMI) was associated with greater efficacy. Overall, the efficacy of DMab was greater in those at moderate to high risk of Fx as assessed by FRAX [101].

A multicenter, international, randomized, double-blind, double-dummy study was conducted in 504 postmenopausal women above 55 years of age with a BMD *T*-score of −2.0 or less and −4.0 or more who had been receiving ALN therapy for at least 6 months (STAND study). Subjects received open-label branded ALN 70 mg once weekly for 1 month and then were randomly assigned to either continued weekly ALN therapy or subcutaneous DMab 60 mg every 6 months and were followed for 12 months. Changes in BMD and BTM were evaluated. In subjects transitioning to DMab, total hip BMD increased by 1.90% at month 12 compared with a 1.05% increase in subjects continuing on ALN ($p < 0.0001$). Significantly greater BMD gains with DMab compared with ALN also were achieved at 12 months at the lumbar spine, femoral neck, and 1/3 radius (all $p < 0.0125$). Median serum CTX levels remained near baseline in the ALN group and were significantly decreased versus ALN ($p < 0.0001$) at all-time points with DMab [102].

Another trial was designed to compare the efficacy and safety of DMab with risedronate (RIS) over 12 months in postmenopausal women who transitioned from daily or weekly ALN treatment and were considered to be suboptimally adherent to therapy. In this randomized, open-label study, postmenopausal women aged ≥55 years received DMab 60 mg subcutaneously every 6 months or RIS 150 mg orally every month for 12 months. Endpoints included percentage change from baseline in total hip BMD (primary endpoint), femoral neck, and lumbar spine BMD at month 12, and percentage

change from baseline in CTX at months 1 and 6. Safety was also assessed. A total of 870 subjects were randomized (435, RIS; 435, DMab) who had a mean (SD) age of 67.7 (6.9) years, mean (SD) BMD *T*-scores of −1.6 (0.9), −1.9 (0.7), and −2.2 (1.2) at the total hip, femoral neck, and lumbar spine, respectively and median CTX of 0.3 ng/ml at baseline. At month 12, DMab significantly increased BMD compared with RIS at the total hip (2.0% versus 0.5%), femoral neck (1.4% versus 0%), and lumbar spine (3.4% versus 1.1%; $p = 0.0001$ at all sites). DMab significantly decreased CTX compared with RIS at month 1 (median change from baseline of −78% versus −17%; $p < 0.0001$) and month 6 (−61% versus −23%; $p < 0.0001$). Overall and serious adverse events were similar between groups. The authors concluded that in postmenopausal women who were suboptimally adherent to ALN therapy, transitioning to DMab was well tolerated and more effective than RIS in increasing BMD and reducing bone turnover [103].

Postmenopausal women with OP were enrolled in a randomized, controlled trial and assigned to receive 20 μg TPD daily, 60 mg DMab every 6 months, or both. BMD was measured at 0, 3, 6 and 12 months. At 12 months, posterior-anterior lumbar spine BMD increased more in the combination group (9.1%, [SD 3.9]) than in the TPD (6.2% [4.6], $p = 0.0139$) or DMab (5.5% [3.3], $p = 0.0005$) groups. Femoral neck BMD also increased more in the combination group (4.2% [3.0]) than in the TPD (0.8% [4.1], $p = 0.0007$) and DMab (2.1% [3.8], $p = 0.0238$) groups, as did total hip BMD (combination, 4.9% [2.9]; TPD, 0.7% [2.7], $p < 0.0001$; DMab 2.5% [2.6], $p = 0.0011$). The authors concluded that combined TPD and DMab increase BMD more than either agent alone and more than has been reported with approved therapies [104].

A few cases of osteonecrosis of the jaw were reported in patients with cancer or in patients with OP treated with DMab [105–107]. Atypical femoral fractures were also described in patients receiving DMab [108,109]. Whereas these cases do not provide conclusive evidence for causal relationship between treatment with DMab and osteonecrosis or unusual sub-trochanteric Fx, other information is now required regarding the long-term safety of this potent inhibitor of bone resorption.

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% [110], the relative molecular weight (anhydrous) is 513.49.

It is the first anti-osteoporotic agent that appears to simultaneously increase bone formation and decrease bone resorption, thus resulting in the creation of new bone [111]. 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 [112–114].

SR has been investigated in a large phase 3 program, initiated in 1996, which includes two clinical trials for the treatment of established OP [113,114]. The SOTI study aimed at assessing the effect of SR on the risk of vertebral Fx [114]. The TROPOS trial aimed to evaluate the effect of SR on peripheral (non-spinal) Fx [113].

In SOTI, a total of 1649 postmenopausal osteoporotic women were randomized to SR or PBO 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 [113] (ITT, $n = 1442$), evaluating the effect of SR 2 g/day on vertebral Fx rates, revealed a 41% reduction in RR of experiencing a new vertebral Fx (semi quantitative assessment) with SR throughout the 3-year study compared with PBO (139 patients with vertebral Fx versus 222, respectively [RR 0.59; 95% CI 0.48–0.73; $p < 0.001$]). The risk of clinical vertebral Fx, 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 Fx was significantly reduced in the SR group as compared with the PBO group for the first year. Over the first 12 months, RR reduction was 49% (RR 0.51; 95% CI 0.36–0.74; $p < 0.001$). In SOTI, the lumbar BMD

increased by 14.4% in the treated group in comparison with the PBO 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 PBO 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 PBO group at month 3 (a treatment-related difference of 12.2%, $p < 0.001$) and at each subsequent evaluation during the 3 years ($p < 0.001$). 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 PBO group, while U-NTX was significantly decreased in the SR group over the 3 years of follow-up [112–114].

The risk of new vertebral Fx over the 4-year treatment period was reduced by 33% with SR, relative to PBO (RR 0.67; 95% CI 0.55–0.81; $p < 0.001$). Similarly, the risk of new clinical vertebral Fx 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 Fx 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 Fx was significantly lower in the SR group (275) than in the PBO group (421; $p < 0.001$). The risk of new clinical vertebral Fx was reduced by 36% with SR relative to PBO (RR 0.64; 95% CI 0.49–0.83; $p < 0.001$) [113].

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 PBO, 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/cm^2) compared with month 0 (0.734 ± 0.123 g/cm^2). Both the increase in lumbar BMD in the group maintained on SR and the decrease in the group switched to PBO between month 48 and the end of treatment were significant ($p < 0.001$ and $p = 0.002$, respectively). BMD in the group switched to PBO 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 of the trial (6.4 ± 7.7%) [115].

The primary analysis of TROPOS (ITT, $n = 4932$), evaluating the effect of SR 2 g/day on non-vertebral Fx, showed a 16% RR reduction in all non-vertebral Fx over a 3-year follow-up period (RR 0.84; 95% CI 0.702–0.995; $p = 0.04$) [114]. SR treatment was associated with a 19% reduction in risk of major non-vertebral osteoporotic Fx (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 Fx 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. The risk of non-vertebral Fx was reduced by 15% in the SR group compared with the PBO group (RR 0.85; 95% CI 0.73–0.99). A post-hoc analysis showed that the risk of hip Fx in a high-risk subset of the population was decreased by 43% (RR 0.57; 95% CI 0.33–0.97; $p = 0.036$), and the risk of vertebral Fx 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 [116].

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 Fx (13.7% and 12.0%, 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 anti-Fx efficacy is sustained over 8 years [117].

Postmenopausal osteoporotic women participating in the double-blind, PBO-controlled phase 3 studies SOTI and TROPOS to 5 years were invited to enter a 5-year open-label extension, during which they received SR 2 g/day ($n = 237$, 10-year population). Bone mineral density (BMD) and Fx incidence were recorded, and FRAX® scores were calculated. The effect of SR on Fx incidence was evaluated by comparison with a FRAX®-matched PBO group identified in the TROPOS PBO arm.

The patients in the 10-year population had baseline characteristics comparable to those of the total SOTI/TROPOS population. Over 10 years, lumbar BMD increased continuously and significantly ($p < 0.01$ versus previous year) with 34.5 ± 20.2% relative change from baseline to 10 years. The incidence of vertebral and non-vertebral Fx with SR in the 10-year population in years 6–10 was comparable to the incidence between years 0 and 5, but was significantly lower than the incidence observed in the FRAX®-matched PBO group over 5 years ($p < 0.05$); relative risk reductions for vertebral and non-vertebral Fx were 35% and 38%, respectively. SR was safe and well tolerated over 10 years [118].

To assess the efficacy of SR according to the main determinants of vertebral Fx 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 [$n = 2536$]; PBO group [$n = 2546$]; average age 74 years; 3-year follow up) [119].

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; $p = 0.03$) Fx. The decrease in risk of vertebral Fx 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 Fx 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 Fx according to the ITT principle [120]. Over 3 years, treatment with SR significantly reduced the risk of vertebral Fx by 43% (RR 0.57; 95% CI 0.36–0.92; $p = 0.019$), with a 16.9% incidence of vertebral Fx in the SR group versus 29.6% in the PBO group. This efficacy in reducing the risk of vertebral Fx 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 Fx of 21.6% in the SR group versus 32.8% in the PBO group.

To determine whether SR also reduces Fx 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 [121]. Yearly spinal X-rays were performed in 895 patients. Only radiographically confirmed non-vertebral Fx were included. Baseline characteristics did not differ in PBO and treatment arms. In the ITT analysis, the risk of vertebral, non-vertebral and clinical (symptomatic vertebral and non-vertebral) Fx 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 Fx 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% 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 Fx observed during the treatment, respectively [122,123].

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 PBO groups [113,114]. During the first 3 months of treatment, nausea, diarrhea, headache, dermatitis and eczema were more frequently associated with SR compared with PBO; but, thereafter, there was no difference in incidence between SR and PBO 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), [124–126].

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 [127]. Age-adjusted rate ratios for VTE, gastrointestinal disturbance, minor skin complaint and memory loss were 1.1 (95% CI 0.2–5.0), 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 [128].

The postmarketing experience of patients treated with SR reported cases of the DRESS syndrome (<20 for 570,000 patient-years of exposure) [129]. This incidence is in the vicinity of what has been previously reported as severe skin reactions with most other currently available anti-OP medications [130]. 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 [131] 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 OP and osteoarthritis [132].

The cardiac safety of the OP treatment SR was explored in the UK Clinical Practice Research Datalink (CPRD). Of the 112,445 women with treated postmenopausal OP, 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 (OR 1.05, 95% 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 CPRD did not find evidence for a higher risk for cardiac events associated with the use of SR in postmenopausal OP [133].

Using the Danish National Prescription Database, a recent survey identified all 3252 patients aged 50+ who began SR in 2005–2007 and 35,606 users of other OP 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, $p = 0.38$]) [134].

In a nationwide cohort study conducted in Denmark, compared with use of ALN/RIS, use of SR was not associated with significantly increased risk of acute coronary syndrome (rate per 1000 person-years: 5.7 for SR versus 6.3 for alendronate/risedronate). Similar results were obtained when looking at patients who had first been treated with a first-line BP and subsequently switched to SR (9.9 per 1000 person-years) or IBN (9.9 per 1000 person-years) [135].

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.

The review of SR benefit/risk evaluation positively ended in February 2014 with the drug being granted a restricted marketing authorization, for the treatment of severe OP, in postmenopausal women and in adult men, at high risk of Fx for whom treatment with other medicinal products approved for the treatment of OP is not possible due to, for example, contraindications or intolerance. The use of SR should be restricted to patients with no past or current history of ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease or uncontrolled hypertension [136,137].

Peptides from the parathyroid hormone family

Peptides from the parathyroid hormone (PTH) family have been investigated in the management of osteoporosis for >30 years [138]. 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) (TPD) 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 Fx, 1637 postmenopausal women with prior spine fractures were randomly assigned to receive 20 or 40 μg of TPD or PBO, 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 Fx occurred in 14% of the women in the PBO group and in 5% and 4% of the women in the 20- and 40-μg dose groups, respectively. The RR of Fx, as compared with the PBO group, was 0.35 and 0.31 (95% CI, 0.22–0.55 and 0.19–0.50), respectively. New non-spine Fx occurred in 6% of the women in the PBO group and 3% of those in each TPD (RR, 0.47 and 0.46, 95% CI, 0.25–0.88 and 0.25–0.86, respectively). TPD had only minor side effects (occasional nausea and headache) [139].

The anti-Fx efficacy of TPD on spine Fx 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 BMD values (*T*-score < -2.5 or > -2.5) or number of prevalent Fx (one or two or more Fx) [140].

At the end of this trial, patients were followed for an additional 18-month period without TPD, during which they were allowed to use any antiosteoporotic 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 PBO group than in the patients having received 20 TPD μg/day, the reduction of spine Fx 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) [141]. A follow up in 1262 women was conducted up to 30 months after discontinuation of treatment. The HR for combined TPD 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 Fx [142].

TPD-mediated relative Fx risk reduction was shown to be independent of pre-treatment bone turnover [143].

The European Forsteo Observational Study (EFOS) was designed to examine the effectiveness of TPD in postmenopausal women with OP treated for up to 18 months in normal clinical practice in eight European countries [144].

All 1648 enrolled women were TPD treatment-naive, 91.0% of them had previously received other anti-OP drugs, and 72.8% completed the 18-month study. A total of 168 incident clinical Fx were sustained by 138 (8.8%) women (821 Fx/10,000 patient-years). A 47% decrease in the odds of Fx 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 endpoint ($p < 0.001$). The largest improvements were reported in the EUROQOL-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 48.0% were considered related to TPD; adverse events were the reason for discontinuation for 79 (5.8%) patients. In conclusion, postmenopausal women with severe OP who were prescribed TPD in standard clinical practice had a significant reduction in the incidence of fragility Fx 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) [144]. In this study, women aged ≥75 years showed a reduced clinical Fx 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 TPD discontinuation when patients were taking other OP medication. The results should be interpreted in the context of an uncontrolled observational study [145,146].

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 TPD lacks, also has biological functions in the bone that are mediated by a novel receptor, specific for this region of the hormone. TPD, 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 [147].

In a Phase II study, women self-administered PTH (50, 75 or 100 μg) or PBO 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 (+2.0%). 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. BTM 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 [148,149]. Evidence from the TOP (Treatment of Osteoporosis with Parathyroid Hormone) study, including women with low BMD (with or without previous Fx) suggest that PTH (1–84) reduced the incidence of vertebral Fx in all patients and prevented the incidence of first vertebral Fx in women with postmenopausal osteoporosis. Reduction of non-vertebral or hip fractures does not clearly appear from the currently available data [149,150].

Once-weekly subcutaneous injections of TPD (56.5 μg) to Japanese osteoporotic women reduced the risk of new vertebral Fx with a cumulative incidence of 3.1% in the TPD group, compared with 14.5% in the PBO group ($p < 0.01$), and a relative risk of 0.20 (95% CI, 0.09–0.45). At 72 weeks, TPD administration increased BMD by 6.4, 3.0, and 2.3% at the lumbar spine, the total hip, and the femoral neck, respectively, compared with the PBO ($p < 0.01$). Adverse events (AE) and the dropout rates by AE were more frequently experienced in the TPD group, but AE were generally mild and tolerable [151].

Significant Fx risk reductions were observed in the subgroups of individuals aged <75 years [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 Fx in the subgroup with 1 (RR 0.08, $p = 0.015$) or ≥2 (RR 0.29, $p = 0.009$) prevalent vertebral Fx, and in those with severe 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 TPD group, no incident Fx was observed in the subgroups with no prevalent vertebral Fx, with mild to moderate vertebral deformity, or with lumbar BMD ≥2.5 SD [152].

A randomized, double-blind trial to assess the effect of 28.2 μg weekly TPD versus PBO (1.4 μg TPD) on reduction of the incidence of vertebral Fx included patients with primary OP with one to five vertebral Fx and capable of self-supported walking. Attention was focused on incident vertebral Fx, 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 Fx occurred in 3.3% of subjects in the 28.2 μg TPD-treated group and 12.6% of subjects in the PBO group during the 78-week study period. Kaplan–Meier estimates of risk after 78 weeks were 7.5 and 22.2% in the TPD and PBO groups, respectively, with a relative risk reduction of 66.4% by TPD ($p = 0.008$). Lumbar BMD in the 28.2 μg TPD group increased significantly by 4.4 ± 4.7% at 78 weeks, which was significantly higher than the corresponding data in the PBO group ($p = 0.001$). Adverse events were observed in 86.7% of individuals in the TPD group and 86.1% of those in the PBO group [153].

In a 6-month, randomized, PBO-controlled, positive control, multidose daily administration studies, 165 postmenopausal women (mean age, 64 year) with OP received a TPD patch with a 20-, 30-, or 40 μg dose or a PBO patch, self-administered daily for 30-min wear time, or 20 μg of TPD injected daily. TPD delivered by transdermal patch significantly increased lumbar spine BMD versus PBO patch in a dose-dependent manner at 6 months ($p < 0.001$). TPD 40-μg patch increased total hip BMD compared to both PBO patch and TPD injection ($p < 0.05$). BTM (PINP and CTX) increased from baseline in a dose-dependent manner in all treatment groups and were all significantly different from PBO patch ($p < 0.001$). All treatments were well tolerated, and no prolonged hypercalcemia was observed [154].

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 PBO arm. Open-label TPD, resulted in a 5.1% increase in lumbar spine 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 [155].

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.

The effect of PTD (20 μg/day) therapy on BMD and bone turnover were assessed in women with OP who were previously treated with either ALN or raloxifene (RLX) therapy for 18–36 months. Median baseline BTM 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% versus prior RLX +0.5%) and at the spine (prior ALN +0.5% versus 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 TPD 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 is 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 [156] 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 TPD in patients treated with an anti-resorptive 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 anti-resorptive agent and an anabolic drug such as TPD together, would provide a therapeutic advantage by combining different mechanisms for the reduction of the risk of Fx. While previously mentioned trials reported the addition of TPD to ongoing ERT/HRT [141], fewer data are available for the use of anti-resorptive 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 [157].

To evaluate the effects of combination therapy including an intravenous infusion of zoledronic acid (ZA) 5 mg and daily subcutaneous TPD 20 μg versus either agent alone on BMD and BTM, a 1-year multicenter, multinational, randomized, partial double-blinded, controlled trial was designed. 412 postmenopausal women with OP (mean age 65 ± 9 years) were randomized to a single infusion of ZA 5 mg plus daily subcutaneous TPD 20 μg ($n = 137$), ZA alone ($n = 137$), or TPD 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%, 7.0%, and 4.4% in the combination, TPD, and ZA groups, respectively ($p < 0.001$ for combination and TPD versus ZA). In the combination group, spine BMD increased more rapidly than with either agent alone ($p < 0.001$ versus both TPD and ZA at 13 and 26 weeks). Combination therapy increased total-hip BMD more than TPD alone at all times (all $p < 0.01$) and more than ZA at 13 weeks ($p < 0.05$), with final 52-week increments of 2.3%, 1.1%, and 2.2% in the combination, TPD, and ZA groups, respectively. The authors concluded that while TPD increases spine BMD more than ZA and ZA increases hip BMD more than TPD, combination therapy provides the largest, most rapid increments when both spine and hip sites are considered [158].

In a randomized, double-blinded study of risedronate (RIS) (35 mg weekly plus PBO injection), TPD (20 μg subcutaneously daily plus PBO tablet), or both RIS plus TPD (combination) for 18 months in 29 men with low BMD, the primary endpoint was percentage change in lumbar spine BMD at 18 months. Secondary outcomes included changes in BTM and BMD at other sites and interim time-points. All therapies increased lumbar spine BMD as compared with baseline ($p < 0.05$), but there were no between-group differences at 18 months. Total hip BMD increased to a greater extent in the combination group (mean ± SEM, 3.86 ± 1.1%) versus TPD (0.29 ± 0.95%) or RIS (0.82 ± 0.95%; $p < 0.05$ for both). Femoral neck 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 TPD alone. In the combination group, P1NP and CTX increased rapidly, mirroring the TPD-alone arm. There were no between-group differences in adverse events. Combination TPD and RIS increased BMD at the lumbar spine, total hip and femoral neck and provided greater BMD increases at the total hip than monotherapy [159]. We previously reported the effects of combined TPD and DMab treatment [104].

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 [157]. 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 TPD, anti-resorptive with RLX, or no active treatment) after 1 year of TPD. Postmenopausal women with OP and a recent fragility Fx received open-label TPD (20 μg/d) for 12 months before they were randomized (3:1:1) to continue TPD ($n = 305$), 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 TPD 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 TPD, 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 [160].

As previously mentioned, several reports suggested that TPD might be interesting addition to the armementarium of atypical femoral Fx associated with long-term use of BP therapy, in postmenopausal osteoporotic women, by improving healing of atypical Fx and restoration of bone quality [79,80,161,162]. It might also improve healing of osteonecrosis of the jaw induced by inhibitors of bone resorption [163].

Conclusion

Several anti-osteoporosis medications were made available since the turn of the century. Physicians have now the choice between several drugs which have, for most of them, shown their ability to reduce Fx rates at the most important skeletal sites (vertebral, non-vertebral and hip). Inhibitors of bone resorption and, more specifically BP, are the most widely prescribed anti-OP drugs worldwide. Their antifracture efficacy is not challenged. However, at least for the most potent of them (i.e. BP and DMab) their potential long-term skeletal toxicity (i.e. osteonecrosis of the jaw and atypical femoral fracture) raises fierce debates on the most appropriate duration of treatment. Selective estrogen receptor modulators, which are mild anti-resorptive agents, do not generate the same concerns but their inability to reduce non-vertebral Fx rates limit their prescription to women with predominantly trabecular OP and low hip Fx risk. Within the peptides from the parathyroid hormone family, TPD is the most commonly used for its ability to stimulate bone formation, hence improving bone strength and reducing Fx at trabecular and cortical sites. Studies using TPD were, however, of limited duration and were not able to demonstrate reduction in hip Fx incidence. TPD is an expensive medication and should be given, sub-cutaneously, on a daily basis; this limits its use to patients with severe OP, in most cases as a second line treatment, after failure or withdrawal of anti-resorptive agents. SR is the only medication currently able to concomitantly reduce bone resorption and simulate bone

formation. It was shown to reduce Fx at all skeletal sites, including hip, in a wide scatter of patients. A recently described increase in the occurrence of non-fatal myocardial infarctions prompted the regulatory agencies to reconsider its benefit/risk in the management of OP. The European Medicines Agency concluded, in February 2014, that SR benefit/risk was still positive but that its use should be restricted to patients at high risk of Fx, for whom treatment with other medicinal products approved for the treatment of OP is not possible, due to, for example, contraindications or intolerance. Patients with established, current or history of ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease or uncontrolled hypertension should not be prescribed SR. Noteworthy all anti-OP medications, but DMab, should be avoided in patients with advanced renal failure (i.e. creatinine clearance below 30 ml/min).

Practice points

- ✓ Bisphosphonates are the most widely prescribed drugs but their adherence is low.
- ✓ From all currently prescribed oral and iv bisphosphonates, zoledronic acid has the highest chance of causing gastrointestinal adverse events.
- ✓ Denosumab is a very potent inhibitor of bone resorption which reduces fractures at all skeletal sites. Its long-term skeletal safety needs to be confirmed.
- ✓ Teriparatide stimulates bone formation and reduces vertebral and non-vertebral fractures in patients with severe osteoporosis. Evidence of hip fracture reduction is not available.
- ✓ Strontium ranelate is an appropriate treatment for patients without cardiovascular contra-indication who cannot or do not want to receive another treatment approved for the management of osteoporosis.
- ✓ Raloxifene is particularly indicated in women with predominantly trabecular osteoporosis at increased risk of breast cancer.

Research agenda

- ✓ New chemical entities, which predominantly affect bone formation, with the potential of short term or intermittent administration, are needed.
- ✓ Combination or sequential treatments should be better investigated.
- ✓ Long-term skeletal safety of inhibitors of bone resorption needs to be better documented.
- ✓ Optimal duration of anti-osteoporosis treatments should be clarified.
- ✓ Treatment acting concomitantly on bone, muscle and cartilage should be developed.

Summary

Inhibitors of bone resorption and, more specifically bisphosphonates, are the most widely prescribed anti-osteoporosis drugs worldwide. However, at least for the most potent of them (i.e. bisphosphonates and denosumab) their potential long-term skeletal toxicity (i.e. osteonecrosis of the jaw and atypical femoral fracture) raises fierce debates on the most appropriate duration of treatment. Selective estrogen receptor modulators are prescribed to women with predominantly trabecular osteoporosis and low hip fracture risk. Teriparatide is an expensive medication and should be given, sub-cutaneously, on a daily basis; this limits its use to patients with severe osteoporosis, in most cases as a second line treatment, after failure or withdrawal of anti-resorptive agents. Strontium ranelate is the only medication able to concomitantly reduce bone resorption and simulate bone formation.

Strontium ranelate use should be restricted to patients at high risk of fracture, for whom treatment with other medicinal products approved for the treatment of osteoporosis is not possible, due to, for example, contraindications or intolerance. Patients with established, current or history of ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease or uncontrolled hypertension should not be prescribed strontium ranelate.

Conflict of interest

Jean-Yves Reginster

Consulting fees or paid advisory boards: Servier, Novartis, Negma, Lilly, Wyeth, Amgen, GlaxoSmithKline, Roche, Merckle, Nycomed-Takeda, NPS, IBSA-Genevrier, Theramex, UCB, Asahi Kasei, Endocyte.

Lecture fees when speaking at the invitation of a commercial sponsor: Merck Sharp and Dohme, Lilly, Rottapharm, IBSA, Genevrier, Novartis, Servier, Roche, GlaxoSmithKline, Merckle, Teijin, Teva, Analis, Theramex, Nycomed, NovoNordisk, Ebewee Pharma, Zodiac, Danone, Will Pharma, Amgen.

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