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Review

Long-term treatment of osteoporosis in postmenopausal women: a review from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) and the International Osteoporosis Foundation (IOF)

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Abstract

Introduction:
Postmenopausal osteoporosis is a chronic disease requiring treatment that balances long-term fracture efficacy against risk.

Methods:
We reviewed the efficacy and safety of calcium and vitamin D, the selective estrogen receptor modulators (SERMs), the bisphosphonates, denosumab, and strontium ranelate in studies of 3 years or longer.

Results:
Six trials lasted for 5 years, and seven went beyond that. The evidence beyond 5 years is generally weak, mainly due to methodological issues (open-label design, small samples, or absence of placebo control). Although calcium and vitamin D appear to be beneficial, the data are insufficient to evaluate benefits and risk beyond 3 years. The fracture efficacy of SERMs beyond 5 years is not known, though increases in bone mineral density (BMD) appear to be maintained. The SERMs have good long-term safety, including protective effects against breast cancer. The bisphosphonates have established fracture efficacy to 3 years, and 4 or 5 years with alendronate and risedronate. The evidence beyond 5 years indicates sustained increases in BMD. The safety of the bisphosphonates does not appear to be modified with time, with the possible exceptions of atypical subtrochanteric fracture and other events of unknown frequency. Denosumab has been tested up to 5 years, with continued increased in BMD and no reported safety issues. There is evidence for fracture efficacy of strontium ranelate, and sustained increases in BMD over 10 years. Strontium ranelate has good long-term safety.

Conclusion:
Robust long-term studies are relatively rare for the osteoporosis treatments, and generally show maintenance of BMD and, for some agents, an additional reduction in fracture incidence.

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Introduction

Nearly a third of all postmenopausal women in Europe have osteoporosis[1], and the absolute number is set to rise with the aging of the population. Well designed, placebo-controlled studies indicate that pharmacological treatment reduces fracture risk by between about 30% and 70% for vertebral fracture and 16% and 25% for non-vertebral fracture[1–3]. The majority of data on fracture effects is from studies of 3 years, as defined by regulatory requirements in Europe and the USA. Evidence for the continued efficacy of treatments in osteoporosis over the long term is often incomplete, though there is some indication that some of the agents currently available in Europe have sustained fracture efficacy beyond the conventional clinical trial limit of 3 years. The aim of this paper was to summarize the evidence base for fracture efficacy in the long term, and weigh this against any long-term adverse effects, in order to guide management decisions.

A key issue is finding the balance between the evidence for long-term efficacy and the probability of adverse events. These concerns are far from confined to the management of osteoporosis, and remain the subject of debate in other therapeutic areas, for example, for lipid-lowering[4,5] and antidiabetic agents[6]. Clearly, any pharmacological treatment should be both efficacious and safe, but the balance between efficacy and safety is not always readily evaluated beyond the normal time limits of randomized controlled trials (RCTs).

The efficacy of an osteoporosis treatment is measured by the reduction in risk for osteoporotic fracture. Surrogate markers for efficacy include bone mineral density (BMD), body height, and biomarkers of bone formation and resorption. A number of factors may impact the long-term efficacy of a treatment in terms of reduction in fracture rate. These include considerations of onset of efficacy after starting treatment, offset in the case of stopping treatment, and intermediate stability. The offset pattern of alendronate, for example, has shown that its impact on BMD may continue for up to 5 years after stopping treatment[7,8].

The long-term efficacy of an agent must be balanced against the probability of adverse effects, serious or otherwise[9]. Data from long-term RCTs should be supplemented with that derived from post-marketing studies, pharmacovigilance, and case reports, particularly for the rarer side effects, which may only be observed when the agents pass into widespread clinical use. A complicating factor in considering the safety profile in individuals with osteoporosis is the comorbidity associated with the disease. For example, osteoporotic women are at increased risk for venous thromboembolism[10], and low BMD is independently associated with peripheral atherosclerosis and cardiovascular events[11] and death.

Long-term clinical trials are by no means simple to carry out in osteoporosis. Current treatment options in osteoporosis have been tested robustly in phase 3 for 3 years and, rarely, to 5 years. Some of these trials have continued in extensions to 8 or 10 years but their reliability decreases with time[12]. The placebo arm is stopped and active treatment offered because of the ethical reasons that arise by retaining at-risk patients on placebo. This precludes definitive conclusions of the effect of a treatment in reducing fracture risk, since it cannot be proved that the gains achieved against placebo continue. A second issue is attrition of trial populations in the long term[13]. Although the fracture risk of a randomized population is expected to be similar between treatment groups at baseline, the randomization may be increasingly eroded between groups receiving active treatment and placebo as the trial progresses. After the occurrence of a fracture, the patient is usually censored from the study (provided, of course, that the treatment is better than placebo). Patients receiving placebo are therefore more likely to be censored from the study, and so, in the long term, the active

treatment group is more likely to contain higher risk patients than the placebo group. This reduces the power to detect the effects of active treatment in an extension phase. Thirdly, open-label extension phases may give a false impression of adverse events, since patients with good tolerance are more likely to opt for continuation of treatment. Finally, the extension phases may include only a small proportion of the original clinical trial population, which also reduces the validity of any conclusions on continued efficacy. Most of the trials that continue beyond 5 years did so in small populations (<130 patients) with the exception of the trials for alendronate, strontium ranelate, denosumab, and raloxifene[7,13–20].

There are currently 13 trials in osteoporosis that exceed 3 years and these are summarized in Figure 1 and Table 1[7,8,13–30]. The trials in this review cover broadly the various therapeutic options in postmenopausal osteoporosis in Europe and are discussed below.

Methods

Relevant articles, reviews, and abstracts were identified through a PubMed/MEDLINE search of English-language articles published between 1990 and September 2011. The search strategy included the terms osteoporosis, osteoporosis treatment, long-term trials (over 3 years), bisphosphonate (alendronate, risedronate, zoledronic acid, ibandronate, pamidronate, clodronate and incadronate), denosumab, SERMs (raloxifene, bazedoxifene, and lasofoxifene), strontium ranelate, teriparatide, and PTH. Separate subsearches were also performed using a cross-search of the above terms combined, as well as the reference lists of the selected articles. Similar searches were also performed for communications at the 2009 to 2011 conferences of the International Osteoporosis Foundation (IOF), the American Society for Bone and Mineral Research (ASBMR), and the European Calcified Tissue Society (ECTS). Overall, 261 items were detected, 129 of which were selected by the authors for inclusion in this review.

Calcium and vitamin D

Calcium and vitamin D are essential for bone health in osteoporosis, usually in combination with an osteoporosis treatment[31,32]. Calcium and vitamin D have a direct impact on calcium absorption, and have been shown to prevent bone loss[33]. Vitamin D also has an effect on neuromuscular function, and supplementation may reduce the risk of falls[34]. The combination of reduced bone loss and fewer falls is expected to reduce the overall risk of fracture. Since the elderly are less capable of adapting to a low calcium diet than the young[35], there is a strong rational for supplementation in postmenopausal osteoporotic women.

Current guidelines recommend calcium and vitamin D intake as part of the management strategy for women with postmenopausal osteoporosis[31,32,36]. The generally recommended dosage of vitamin D is 800 to 1000 IU per day, while calcium supplementation in postmenopausal women should target 700 to 1000 mg/day, according to country due to regional dietary habits. The general assumption is that supplementation should continue long term, concomitant to treatment with osteoporosis treatments.

Long-term fracture efficacy

Fracture risk reduction over 3 years

The clinical trial evidence for fracture reduction with calcium and vitamin D intake for up to 3 years is far from clear. Some analyses report a significant decrease in fracture risk[37–43], whilst others report a neutral effect[44,45] or even an increase in fracture risk[46]. A meta-analysis of the vitamin D trials concluded that treatment with vitamin D was associated with a dose-dependent reduction in fracture[42]. On the other hand, a patient-level pooled analysis of 68,500 patients in the major vitamin D fracture trials found no effect of vitamin D alone on fracture risk[47]. The combination of calcium and vitamin D reduced all fractures by 12% ($P = 0.025$) and hip fractures by 26% ($P = 0.005$), independently of age, sex, or the presence of previous fractures[47].

A meta-analysis of 17 trials in more than 50,000 patients receiving calcium alone or calcium combined with vitamin D reported a modest effect on the risk of fracture (at any site, including hip, vertebra, or wrist)[41]. Supplementation was associated with a 12% reduction in risk of fracture (relative risk [RR], 0.88, 95% confidence interval [CI] 0.83–0.95). The addition of vitamin D did not bring about a substantial modification of risk (10% reduction in fracture with calcium alone versus 13% with calcium and vitamin D). Trials with good compliance had significantly greater reductions in risk, for example, in the eight trials with compliance rates >80%, the fracture risk reduction was 24%[41], reinforcing the notion of the importance of compliance on clinical outcomes[45].

Fracture risk reduction beyond 3 years

To our knowledge there are no long-term data for vitamin D, and there is one trial of calcium to 5 years. This randomized, double-blind, placebo-controlled trial of calcium supplementation was carried out in 1460 postmenopausal women (Table 1, Figure 1)[23]. In the intention-to-treat analysis, 1200 mg/day calcium failed to significantly reduce risk of clinical osteoporotic fracture versus placebo (hazard ratio [HR], 0.87, 95% CI, 0.67–1.12).

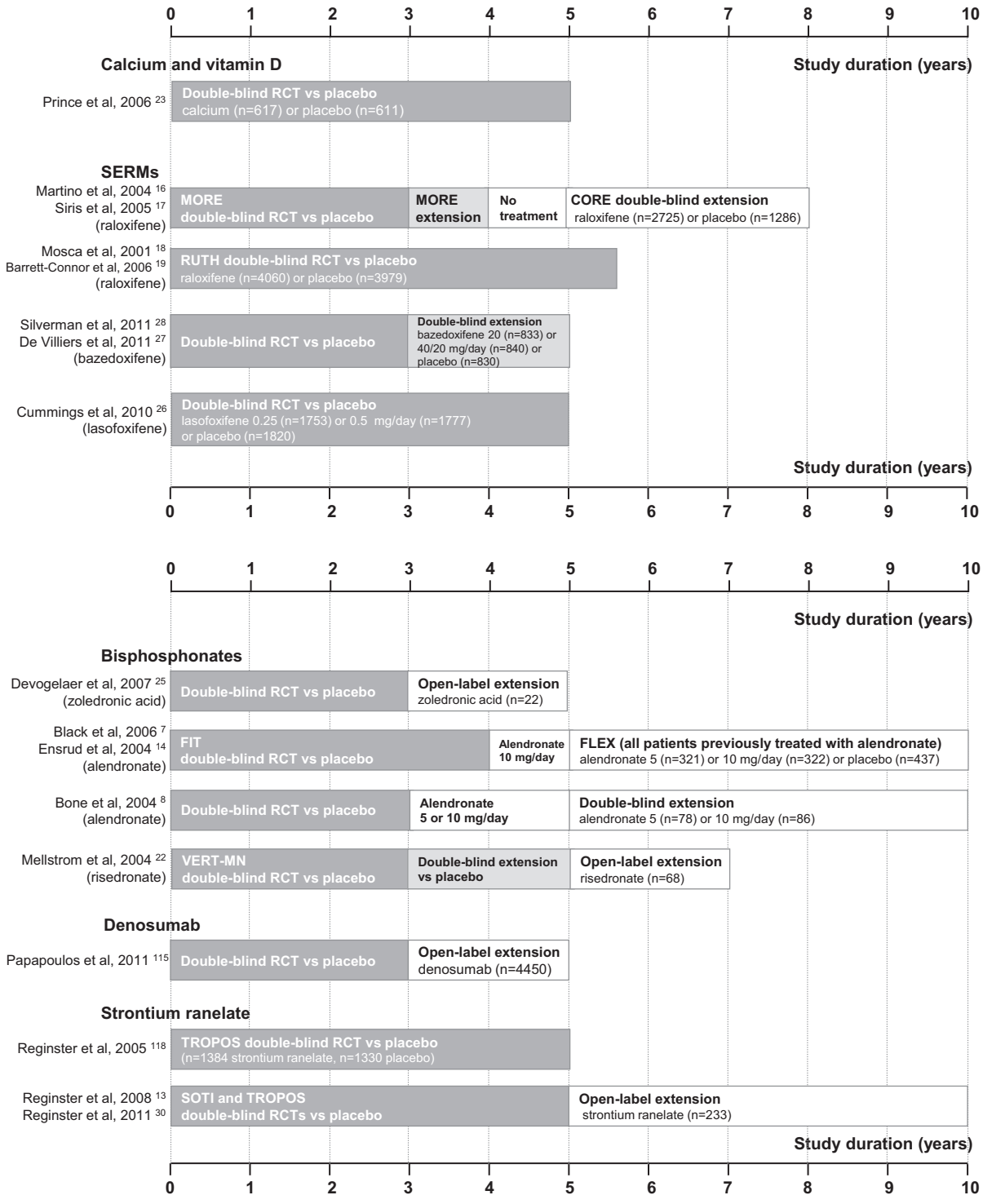

Figure 1. Summary of published study designs for the long-term trials with osteoporosis treatments with fracture-related end points, including the number patients completing the longest treatment period[7,8,13–30]. The pivotal trials are shown in dark gray and the extension phases in white. CORE, Continuing Outcomes Relevant to Evista; FIT, Fracture Intervention Trial; FLEX, Fracture Intervention Trial Long-term EXtension; MORE, Multiple Outcomes of Raloxifene Evaluation; RCT, randomized controlled trial; PEARL, Postmenopausal Evaluation and Risk-Reduction with Lasofoxifene; RUTH, Raloxifene Use for the Heart; SOTI, Spinal Osteoporosis Therapeutic intervention; TROPOS, Treatment of Peripheral Osteoporosis; VERT-MN, Vertebral Efficacy with Risedronate Therapy–Multinational.

Table 1. Summary of results of the published long-term trials (beyond 3 years) with osteoporosis treatments with fracture-related end points.

Treatment	Study	No of patients completing follow-up	Duration	Primary end point	Osteoporosis-related secondary end points	Summary of outcome in terms of fracture efficacy
Studies with fractures as primary end point						
Strontium ranelate	TROPOS[13]	$n=1384$, strontium ranelate 2 g/day $n=1330$, placebo	5 years	Non-vertebral fracture	VF, hip fracture, BMD	Significant reductions in non-vertebral fracture, VF, and hip fracture vs placebo, including in the elderly; sustained increases in BMD
Risedronate	VERT-MN[21]	$n=115$, risedronate 5 mg/day $n=105$, placebo	5 years	Vertebral fracture	Non-vertebral fracture, BMD	Inconclusive (sustained reductions in VF in 4th and 5th years, vs first 3 years); sustained increase in BMD
Calcium	Prince *et al.*[23]	$n=617$ calcium 1200 mg/day $n=611$ placebo	5 years	Clinical osteoporotic fracture, vertebral deformity	Bone structure	Inconclusive (no difference in fracture rate vs placebo)
Lasofoxifene	PEARL study[26]	$n=1753$ lasofoxifene 0.25 mg/day $n=1777$ lasofoxifene 0.5 mg/day $n=1820$ placebo	5 years	Vertebral fracture, non-vertebral fracture, breast cancer	Hip fracture	Significant reductions in vertebral and non-vertebral fracture
Bazedoxifene	Silverman *et al.*[28] De Villiers *et al.*[27]	$n=833$ bazedoxifene 20 mg/day $n=840$ bazedoxifene 40/20 mg/day $n=830$ placebo	5 years	Vertebral fracture	Non-vertebral fracture, BMD	Significant reductions in vertebral fracture
Risedronate	VERT-MN[22]	$n=68$, risedronate 5 mg/day	7 years	Vertebral fracture	Non-vertebral fracture, BMD	Inconclusive (similar reductions in VF in 4th and 6th years); sustained increase in BMD
Strontium ranelate	Reginster *et al.*[117]	$n=233$, strontium ranelate 2 g/day	10 years	Incidence of fracture	BMD	Inconclusive (sustained reductions in fracture in 6th to 10th years, vs first 5 years); sustained increase in BMD
Denosumab	Papapoulos *et al.*[111]	$n=4450$, denosumab 60 mg sc/6 months	5 years	Incidence of fracture	BMD	Inconclusive (sustained reductions in fracture in 3 rd to 5th years, vs first 3 years); sustained increase in BMD
Studies with BMD as primary end point						
Zoledronic acid	Devogalaer *et al.*[25]	$n=22$, zoledronic acid 4 mg once yearly	5 years	BMD	Fracture events	No information on fracture efficacy (no placebo group, small population); sustained increase in BMD
Denosumab	Miller *et al.*[20]	$n=200$, denosumab 60 mg once every 6 months	6 years	BMD	Bone markers	Continued increases in BMD
Alendronate	FLEX[7,14]	$n=321$, alendronate 5 mg/day $n=322$, alendronate 10 mg/day	10 years	Total hip BMD	Fracture incidence, BMD at other sites	No information on fracture efficacy (no placebo group); sustained increase in BMD
Alendronate	Bone *et al.*[8,24]	$n=78$, alendronate 5 mg/day $n=86$, alendronate 10 mg/day	10 years	Lumbar spine BMD	Height (surrogate measure of new VF)	No information on fracture efficacy (no placebo group); sustained increase in BMD

(continued)

Table 1. Continued.

Treatment	Study	No of patients completing follow-up	Duration	Primary end point	Osteoporosis-related secondary end points	Summary of outcome in terms of fracture efficacy
Studies with non-osteoporosis-related end points						
Raloxifene	RUTH[18,19]	$n = 4060$, raloxifene 60 mg/day $n = 3979$, placebo	5.6 years	Coronary death, nonfatal MI, or HACS	Clinical VF or non-vertebral fractures	Significant reduction in clinical VF vs placebo
Raloxifene	CORE[16,17]	$n = 2725$, raloxifene 60 mg/day $n = 1286$, placebo	8 years	Risk of invasive breast cancer	Non-vertebral fracture, VF, BMD	Inconclusive (no difference in fracture rate vs placebo); sustained increase in BMD

BMD, bone mineral density; CORE, Continuing Outcomes Relevant to Evista; FIT, Fracture Intervention Trial; FLEX, Fracture Intervention Trial Long-term EXtension; HACS, hospitalization for acute coronary syndrome; MI, myocardial infarction; PEARL, Postmenopausal Evaluation and Risk-Reduction with Lasofoxifene; RUTH, Raloxifene Use for the Heart; SOTI, Spinal Osteoporosis Therapeutic Intervention; TROPOS, Treatment of Peripheral Osteoporosis; VERT-MN, Vertebral Efficacy with Risedronate Therapy–Multinational; VF, vertebral fracture.

Compliance was again an issue in this trial, since fracture risk was reduced in the participants who were >80% compliant (57% of the sample). The conclusion of the authors was that calcium supplementation is ineffective in improving fracture risk due to poor long-term compliance[23].

Other long-term health benefits or adverse effects

Treatment with calcium and vitamin D may have a number of positive health benefits additional to the reduction of risk of fracture. As mentioned, meta-analysis of eight double-blind RCTs in individuals aged over 65 years showed that vitamin D supplements at 700 to 1000 IU/day reduced the risk of falls by 19%[34]. Supplementation with calcium and vitamin D also appears to prevent tooth loss in the elderly[48]. An RCT in 145 healthy subjects aged 65 years or older reported loss of one or more teeth in 13% of individuals receiving supplementation versus 27% of controls over 3 years (odds ratio [OR], 0.4, 95% CI, 0.2–0.9). In a 2-year extension phase of this study, in which supplementation was withdrawn, subjects who elected to continue nutritional supplements and had calcium intakes of at least 1000 mg/day remained less likely to lose teeth (40% versus 59%, OR, 0.5, 95% CI, 0.2–0.9).

A preliminary report suggested an effect of combined calcium and vitamin D on mortality, with a 12% reduction in participants in five major randomized fracture trials (hazard ratio [HR], 0.88, 95% CI, 0.81–0.97)[49,50]. This reduction in mortality was not accounted for by the prevention of hip fracture. This is in line with other evidence from observational studies that vitamin D protects against cardiovascular disease[51,52], though there currently remain insufficient RCT data for a definitive conclusion on this effect.

As regards adverse effects, calcium supplementation may provoke mild gastrointestinal disturbances, for example, constipation, flatulence, nausea, gastric pain, and diarrhea, and interfere with the absorption of iron and zinc[33]. An RCT indicated an association between long-term calcium supplementation and an increase in cardiovascular events including myocardial infarction (RR, 2.12, 95% CI, 1.01–4.47)[53], possibly due to vascular calcification. This has been confirmed by a recent meta-analysis of 11 trials including about 12,000 participants over an average of 4 years, in which calcium supplementation was associated with a 30% increase in myocardial infarction (HR, 1.27, 95% CI, 1.01–1.59)[54]. The same analysis also reported a smaller, but nonsignificant, impact of calcium supplementation on stroke and mortality. In this meta-analysis, cardiovascular side effects were mostly observed in the patients with spontaneous calcium intake above the median. On the other hand, an RCT of calcium

supplementation in nearly 1500 women recruited from the general population indicated no increase in atherosclerotic disease[55]. These reports have been the subject of considerable debate in the literature regarding whether the magnitude of the effect negates the use of calcium for bone health[56].

Comment

Whereas supplementation with combined calcium and vitamin D at recommended levels appears to be beneficial in terms of fracture efficacy, there are insufficient long-term data to make a definitive conclusion regarding the benefits and risk of supplementation beyond 3 years. Efforts should be made to optimize adherence to treatment, since poor compliance is a significant factor in reducing the efficacy of long-term supplementation. The evidence for increased cardiovascular risk with calcium supplementation and cardiovascular protection with vitamin D remains mixed. On the other hand, as pointed out recently[54], since calcium and vitamin D supplementation is recommended for all patients with osteoporosis, independently of their concomitant osteoporosis treatment, then even modest changes in cardiovascular events may be an important consideration in terms of public health.

SERMs

The selective estrogen receptor modulators (SERMs, raloxifene, bazedoxifene, and lasofoxifene)[57] have agonistic effects in bone in postmenopausal women, which increases BMD and reduce risk of vertebral fracture. On the other hand, they have antagonistic effects on endometrial and breast tissue[58].

Fracture efficacy up to 5 years

There are four trials of raloxifene lasting between 3 and 5 years in the prevention of osteoporotic fracture or invasive breast cancer. The MORE (Multiple Outcomes of Raloxifene Evaluation) trial was a pivotal 3-year, randomized, placebo-controlled trial in nearly 8000 postmenopausal osteoporotic women[59]. Raloxifene (60 mg/day) reduced the risk for vertebral fracture over 3 years (RR, 0.70, 95% CI, 0.5–0.8), but did not reduce the risk for non-vertebral fracture[59]. Similar results were found in an extension of MORE to 4 years[60].

Two 5-year raloxifene trials have been reported in non-osteoporotic women: the North American and European Prevention Trials[61] and STAR (Study of Tamoxifen and Raloxifene)[62]. The Prevention Trials examined the effect on BMD in healthy postmenopausal women receiving raloxifene 60 mg/day ($n = 185$) or placebo ($n = 143$) for 5 years[61]. Raloxifene was found to maintain BMD, reducing the likelihood of the onset of osteoporosis. There was no report of fracture outcomes. The STAR trial included nearly 20,000 women at risk for breast cancer who were randomized to raloxifene 60 mg/day or tamoxifen 20 mg/day[62]. The primary end point was the incidence of coronary events (coronary death, nonfatal myocardial infarction, or acute coronary syndromes) or invasive breast cancer. The incidence of vertebral and non-vertebral fracture was included as a secondary end point, for which there was no difference between the treatments over 5 years (RR, 0.92, 95% CI, 0.69–1.22). The absence of a difference in fracture rate between raloxifene and tamoxifen in STAR[62] is most likely due to a beneficial skeletal effect of tamoxifen[63].

Long-term trials have been performed with lasofoxifene[26] and bazedoxifene with fracture efficacy as an endpoint (Table 1, Figure 1)[27,28]. The fracture efficacy of lasofoxifene has been demonstrated over 5 years in more than 8500 postmenopausal osteoporotic women in the PEARL (Postmenopausal Evaluation and Risk-Reduction with Lasofoxifene) study[26]. At the dosage of 0.5 mg/day, lasofoxifene was found to reduce vertebral fracture (HR, 0.58, 95% CI, 0.47–0.70) and non-vertebral fracture (HR, 0.76, 95% CI, 0.64–0.91) over 5 years[26].

Bazedoxifene has been shown to have anti-fracture efficacy to 3 years in a trial in nearly 7000 postmenopausal women with osteoporosis[64]. The 5-year, placebo-controlled preplanned extension of this study in 3146 patients has recently been published, with consistent results for the longer-term trial[27,28]. Treatment with bazedoxifene was associated with a lower incidence of new vertebral fracture versus placebo over 5 years at the dosage of 20 mg/day (HR, 0.65, 95% CI, 0.46–0.91), though there was no between-group difference in incidence of non-vertebral fracture.

Fracture efficacy beyond 5 years

CORE (Continuing Outcomes Relevant to Evista) was a randomized placebo-controlled extension of MORE including just over 4000 postmenopausal osteoporotic women providing 8 years of observation[16,17] (Table 1, Figure 1). There was a short break between the two studies, and the median time between the end of MORE and enrollment in CORE was 10.6 months. The MORE randomization was maintained in CORE, with 1286 women continuing on placebo and 2725 continuing on raloxifene 60 mg/day (whatever the dosage in MORE). There was no difference in incidence of new non-vertebral fracture with raloxifene (22.8%) versus placebo (22.9%) over 8 years (HR, 1.00, 95% CI, 0.82–1.21)[17], except in patients with pre-existing vertebral fracture in whom risk was decreased (HR, 0.78, 95% CI, 0.63–0.96).

The CORE study had a number of limitations for fracture risk assessment, the most important of which was its original design as a trial to assess the long-term impact of raloxifene on incidence of breast cancer. This meant that there were no scheduled spine radiographs. Another limitation was the attrition of the CORE population, which meant that the study groups were imbalanced at the beginning of CORE[17]. Finally, the concomitant use of bone-active agents was not prohibited from the fourth year onward during the MORE study[60], and so there may also have been some imbalance between the placebo and active treatment groups in this regard.

The RUTH (Raloxifene Use for The Heart) trial lasted 5.6 years (range 0.01 to 7.06 years) (Table 1, Figure 1) in more than 10,000 postmenopausal women at risk of coronary heart disease[18,19]. There was no information on osteoporosis status at baseline. Participants were randomly assigned to raloxifene 60 mg/day ($n = 5057$) or placebo ($n = 5044$). The RUTH results support a reduction in clinical vertebral fracture (HR, 0.65, 95% CI, 0.47–0.89)[19], even though fractures were not the primary end point and it is not possible to determine whether fractures were new or pre-existing.

Long-term safety

The safety assessment of raloxifene in CORE supports the clinical safety of this agent over 8 years[65,66]. Hot flushes and leg cramps are more frequent with raloxifene (with an incidence described by the European Medicines Agency [EMEA] as very common, ≥1/10, and common, ≥1/100, respectively[66]). There was no increased incidence of ovarian cancer, uterine cancer, endometrial hyperplasia, or postmenopausal bleeding in the long-term trials[61,65], though there was an increase in uterine polyps in CORE (3.2% with raloxifene versus 1.9% with placebo, $P = 0.028$)[65].

Raloxifene therapy is associated with a significant reduction in incidence of invasive breast cancer in both CORE and RUTH[16,67]. In CORE, the reduction of risk varied according to baseline risk factors from 89% (HR, 0.11, 95% CI, 0.03–0.38) in women with a family history of breast cancer to 33% (HR, 0.67, 95% CI, 0.23–1.92) in women considered at low 5-year risk on the Gail assessment[67]. The STAR study showed raloxifene to be similar to tamoxifen in terms of reduction in incidence of invasive breast cancer[62]. The CORE results also indicated that raloxifene protected against all cancers, even if breast cancer was excluded[65]. Similar results were reported in STAR[62].

There was no evidence of a long-term increase in cardiovascular risk in CORE[68] or RUTH[19], which is particularly relevant since RUTH was specifically designed to determine the effects of raloxifene on cardiovascular events. There was no difference between raloxifene and placebo in terms of all-cause or total stroke mortality, though there was an increased risk of fatal stroke in the raloxifene group (HR, 1.49, 95% CI, 1.00–1.95)[19]. On the other hand, there was a trend to reduced risk of hemorrhagic stroke with raloxifene in RUTH (HR, 0.59, 95% CI, 0.33–1.06)[19].

Treatment with raloxifene was associated with an increased risk of venous thromboembolism in both CORE (RR, 1.7, 95% CI, 0.9–3.1)[65] and RUTH (HR, 1.44, 95% CI, 1.06–1.95)[19]. An early increase in venous thromboembolism was reported in MORE, with a greater risk in the first 2 years[69]. There was no evidence of an increase in events after restarting raloxifene in the CORE study. The EMEA considers venous thromboembolism as uncommon with raloxifene with an incidence of between ≥1/1000 and ≥1/100[66].

As regards the other SERMs, 5 years' treatment with lasofoxifene was also associated with lower risk for breast cancer, coronary heart disease and stroke, but a higher risk for venous thromboembolic events[26]. Similarly, although venous thromboembolic events were more frequent in the treatment groups, the safety and tolerability profile of bazedoxifene was not modified in the extension trial versus the 3-year trial, and was found to be acceptable[27,28].

Comment

The vertebral fracture efficacy of SERMs has been proven to 4 and 5 years[26–28,59,60]. Beyond that, it is difficult to make definitive conclusions regarding the fracture efficacy of SERMs in postmenopausal osteoporosis. Raloxifene appears to have a good long-term safety profile, and may even have protective effects against breast cancer. Adherence rates at 12 months are poor, but are comparable to adherence to bisphosphonates, and may affect the long-term impact of treatment[70].

Bisphosphonates

Bisphosphonates are stable analogues of pyrophosphate. They have a strong affinity for bone apatite and are potent antiresorptive treatments. Variations in binding affinity and antiresorptive potency lead to differences in onset and offset of effect, degree of reduction in bone turnover, and uptake in cortical or trabecular bone, and may underlie variations in clinical efficacy within the class.

Fracture efficacy between 3 and 5 years

Clinical trials report reductions in the risk of between 40% and 70% for vertebral fracture, 30% and 40% for non-vertebral fracture, and 30% to 40% for hip fracture[2,3]. All the bisphosphonates have proven efficacy against vertebral fracture to 3 years. Efficacy has been demonstrated

for oral alendronate over 3 or 4 years in FIT (Fracture Intervention Trial) for women with and without pre-existing fracture[71–73], for oral risedronate over 3 years in VERT (Vertebral Efficacy with Risedronate Therapy)[74,75], for oral ibandronate over 3 years in BONE (Oral Ibandronate Osteoporosis Vertebral Fracture Trial)[76], and for intravenous (IV) zoledronic acid over 3 years in HORIZON (Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly)[77]. Efficacy for non-vertebral fracture over 3 years has been reported with alendronate in the FIT trial[71], risedronate in VERT[74,75] and HIP (Hip Intervention Program)[78], and zoledronic acid in HORIZON[77]. There is no evidence for efficacy for non-vertebral fracture for ibandronate.

There are two extension trials with observations to 5 years. One was a 2-year placebo-controlled extension of the VERT-MN study in which 220 postmenopausal women completed 5 years of treatment with risedronate 5 mg/day ($n = 105$) or placebo ($n = 115$) (Table 1, Figure 1)[21]. This represented only about a third of the subjects completing 3 years in the original study[75]. The reduction in vertebral fracture between 4 and 5 years of treatment (59%, 95% CI, 19%–79%) was consistent with that observed in the first 3 years (49%, 95% CI, 27%–64%)[21]. The effects of risedronate on BMD were also maintained during the extension phase. One limitation of this study was the small number of participants.

The other 5-year trial was an open-label extension of the phase 2 trials for IV zoledronic acid (Table 1, Figure 1)[25]. Only 22 patients continued in this part of the study and received once-yearly injections of 4 mg zoledronic acid for 5 years years. Two patients (9%) sustained a fracture in the extension phase. Patients treated for 5 years appeared to maintain the increase in BMD and the decrease in bone markers observed at 3 years[25]. This small study with no placebo control was unable to make any definitive conclusions on the impact of zoledronic acid on fracture risk over 5 years.

The results of the 2-year extension of the MOBILE (Monthly Oral Ibandronate in Ladies) study, in which patients received oral ibandronate 100 mg monthly ($n = 176$) or 150 mg monthly ($n = 176$) for 5 years, have been reported in the form of an abstract[79]. The findings suggest sustained increases in BMD both the lumbar spine and hip, but do not include fracture data.

Fracture efficacy beyond 5 years

There are two trials of oral alendronate to 10 years, both in relatively small populations. FLEX (Fracture Intervention Trial Long-term EXtension) was an extension of the FIT trial to 10 years (Table 1, Figure 1)[7,14]. At the end of 4 years in FIT, all patients could opt for a 1-year treatment with alendronate 10 mg/day, after which those who had received 5 years of alendronate were invited to enter FLEX. A total of 643 patients received alendronate 5 or 10 mg/day for a total of 10 years, while 437 patients who had received alendronate for 5 years were switched to placebo for 5 years. FLEX demonstrated that alendronate maintained total hip BMD above pretreatment levels.

The FLEX trial had a number of significant limitations. Although there was a placebo group in FLEX, they had all received alendronate for the first 5 years of the study and so they could not serve as a comparator for long-term fracture efficacy. The FLEX investigators used this group to demonstrate the absence of a significant effect of continuing versus discontinuing alendronate beyond 5 years in terms of cumulative risk of non-vertebral fractures (19% versus 18.9%, respectively)[7]. Continuing versus discontinuing alendronate for 10 years was associated with a significantly lower risk of clinical vertebral fracture (2.4% versus 5.3%, RR, 0.45, 95% CI, 0.24–0.85), but not morphometric vertebral fractures (9.8% versus 11.3%, RR, 0.86, 95% CI, 0.60–1.22). These results fueled a debate in the literature regarding the residual effects of bisphosphonate treatment if treatment is withdrawn after 5 years[80–82]. Finally, a recent complementary analysis of the FLEX trial[83] reported that, among the 720 women without vertebral fracture at FLEX baseline (i.e. after 5 years of treatment), continuation of alendronate reduced non-vertebral fracture in women with FLEX baseline T-score less than -2.5 (RR, 0.50, 95% CI, 0.26–0.96), but not with T-score between -2.5 and -2 (RR, 0.79, 95% CI, 0.37–1.66) or with T-score above -2 (RR 1.41, 95% CI, 0.75–2.66) ($P = 0.019$ for interaction). While these results might appear promising, the FLEX investigators failed to detect an impact of prolonged alendronate treatment on patients with prevalent fracture at FLEX baseline[83]. This is an important drawback to the study since patients with prevalent fracture may be more representative of the general population with osteoporosis.

Alendronate was also studied for 10 years in an extension of two 5-year phase 3 trials, in which postmenopausal women with osteoporosis received alendronate 5 mg/day ($n = 78$) or 10 mg/day ($n = 86$) for 10 years (Table 1, Figure 1)[8,24,84]. No patients received placebo over the whole 10 years, precluding any comparison of efficacy. The primary end point of this study was lumbar spine BMD, for which increases in the first 5 years were sustained over 10 years.

A 2-year, open-label extension of VERT-MN (VERT-Multinational) reported rates of vertebral fracture in a small population of 68 patients who had received oral risedronate 5 mg/day for 7 years (Table 1, Figure 1)[22]. The authors concluded that there was no loss in fracture efficacy over 7 years on the basis of a comparison of the rate of vertebral fracture during the period between 6 and 7 years (3.8%) and that between 4 and 5 years of treatment (4.5%). There were also sustained increases in BMD in the

2-year extension. The absence of a placebo group in this small study precluded any definitive conclusions on long-term fracture efficacy of risedronate.

The preliminary results of a long-term extension of the HORIZON study have been reported in the abstract form. The findings suggest that BMD levels remain constant in the period between 3 and 6 years in the 616 patients continuing on treatment[85].

The two 10-year alendronate studies and the 7-year risedronate study have many weaknesses. Firstly, the incidence of fractures was not a primary end point in any of the studies. Second, comparison with a placebo control group was not possible, either because the extension was only proposed to patients in the treatment arms, or because the placebo patients in the original trial were switched to treatment (or vice versa) and any fracture results may be confounded by the residual effect of bisphosphonate on bone. Thirdly, whilst the original studies were performed in sizable populations, the extension trials included relatively small numbers of patients. The overall conclusions are that increases in BMD with oral bisphosphonates are maintained upon continued long-term therapy, and that the incidence of fracture is not increased[7,8,22].

Long-term safety

The long-term bisphosphonate trials report no long-term safety issues, and there are few data on the links between potential side effects and the duration of treatment[81,86]. However, the bisphosphonates have been associated with a number of rare, but serious, adverse effects, which need to be considered[9,80,82].

Trial evidence suggests an increase in serious adverse events related to atrial fibrillation with zoledronic acid and alendronate, but not risedronate or ibandronate[9]. Serious atrial fibrillation was more frequent in HORIZON over 3 years patients receiving zoledronic acid than placebo (1.3% versus 0.5%, $P<0.001$)[77]. However, in the HORIZON, there was no difference between the treated group and the placebo group for either total or severe atrial fibrillation[77]. The 6-year data appear to confirm this observation[85]. A reanalysis of the FIT trial indicated a trend toward increased atrial fibrillation with alendronate versus placebo over 4 years (1.5% versus 1.0%, $P=0.07$)[87]. The EMEA reports the incidence of atrial fibrillation as common ($\geq$1/100) with alendronate[88]. Meta-analyses and case series analysis have produced inconsistent conclusions[89–93], and there is no robust evidence that long-term treatment increases risk[81].

There is no information regarding a relationship between osteonecrosis of the jaw and treatment duration. There was no treatment–placebo difference in any of the long-term trials, most likely due to the low rate of this adverse event (estimated at between 1 in 10,000 and <1 in 100,000)[94–96]. Higher rates (between 1% and 10%) have been reported in oncology, in which patients are exposed to higher intravenous; in one comparison of zoledronic acid and denosumab, osteonecrosis of the jaw occurred in 1.4% of patients treated with zoledronic acid for cancer[97]. Osteonecrosis of the jaw has already been discussed by ESCEO[98], and an American Society for Bone and Mineral Research (ASBMR) Task Force has set out recommendations for long-term bisphosphonate therapy, which mainly concern invasive dental procedures[94].

By contrast, there may be a relationship between long-term treatment and the occurrence atypical fracture, particularly of the subtrochanteric region of the hip. Reports of this rare adverse event have been attributed to the long-term suppression of bone turnover and accumulation of microdamage in bone[99–101], though the frequency is unknown[102–104]. A related effect is the possibility of delayed fracture healing in treated patients[82,105]. In one small retrospective review of 25 patients receiving alendronate, the average duration of treatment was significantly longer in patients with atypical fracture than in those with a normal fracture pattern (6.9 versus 2.5 years, $P=0.002$)[106].

In 2008, the EMEA concluded that there was an association between atypical subtrochanteric fracture and long-term use of alendronate, and requested a modification of SPC for that agent. A recent ESCEO review of the subject concurred that there is evidence that long-term use of alendronate may increase the risk for atypical, low-trauma subtrochanteric fractures[107]. On the other hand, it remains unclear whether this increased risk also applies to risedronate, ibandronate, and zoledronic acid. A recent report from an American Society for Bone and Mineral Research (ASBMR) task force came to similar conclusions[108], suggesting that the risk increases with the duration of treatment. These concerns are reflected by recent decisions from the EMEA and Food and Drug Administration (FDA) regarding label changes for the bisphosphonates.

The ASBMR task force also highlighted concerns that underreporting and lack of awareness could hide the true extent of the problem[108]. Indeed, the estimated event rate of 1 per 1000 per year is so low that RCTs are unlikely resolve the issue, and more research is necessary from prospective observational studies, meta-analyses, and nested case control studies. The overall conclusion of ESCEO was that currently available evidence does not suggest that the benefits of treatment with bisphosphonates are outweighed by the risk of atypical, low-trauma subtrochanteric fractures[107].

Comment

Fracture evidence is available for all the bisphosphonates to 3 years, and to 4 or 5 years in rare cases for vertebral

fracture for alendronate, risedronate, and zoledronic acid. The strength of the evidence beyond 5 years is relatively weak, mainly due to methodological issues (i.e., open-label studies in small populations with no placebo control). These trials demonstrated that increases in BMD with oral bisphosphonates alendronate and risedronate are maintained to 10 years, but failed to show any effect on the rate of fracture. One feature of long-term treatment is the aging of the target patient population. In this context, we should note that none of the bisphosphonates have proven efficacy against fracture in the elderly aged ≥80 years[109]. The evidence should also be considered alongside the known low rates of adherence in bisphosphonate-treated women beyond 2 years[70,110].

As regards long-term adverse effects, there is no evidence that the safety profile of the bisphosphonates is modified with time, with the possible exceptions of atypical fracture and other events for which the frequency is not known and further monitoring is necessary. For instance, a very recent study reported that long-term alendronate does not cause thickened femoral cortices in 86 patients treated for a mean of 7.3 years[111]. The EMEA and FDA have called for more research in this field, particularly into assessing the incidence of osteonecrosis of the jaw and atypical subtrochanteric fractures in association with dose and duration of use of bisphosphonates[112].

Denusomab

Denosumab is a fully human monoclonal antibody against the RANK ligand and inhibits osteoclast-mediated bone resorption, which gives it a potent antiresorptive activity.

Fracture efficacy between 3 and 5 years

The efficacy of denosumab in the prevention of fracture over 3 years in postmenopausal osteoporosis was demonstrated versus placebo in the FREEDOM (Fracture Reduction Evaluation of Denosumab in Osteoporosis every 6 Months) trial[113]. The FREEDOM trial enrolled 7868 women who received subcutaneous denosumab (60 mg) or placebo every 6 months, and demonstrated reductions in risk for vertebral, non-vertebral, and hip fracture versus placebo. Participants who completed FREEDOM were eligible to enter an extension to continue the evaluation of denosumab efficacy and safety for up to 5 years (Table 1, Figure 1)[29]. Women from the FREEDOM denosumab group had two more years of denosumab treatment (long-term group) and those from the FREEDOM placebo group had 2 years of denosumab exposure (cross-over group). A total of 4550 women enrolled in the extension (2343 long-term; 2207 cross-over). Reductions in bone turnover markers were maintained (long-term group) or occurred rapidly (cross-over group) following denosumab 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 denosumab treatment. Yearly fracture incidences for both groups were below rates observed in the FREEDOM placebo group and below rates projected for a 'virtual untreated twin' cohort. Adverse events did not increase with long-term denosumab administration. Two adverse events in the cross-over group were adjudicated as consistent with osteonecrosis of the jaw (ONJ)[29].

Fracture efficacy beyond 5 years

A phase 2 trial of denosumab has reported long-term data to 4 and 6 years[20,114]. A total of 178 patients completed the 6 years of this open-label, single arm extension study, during which they received 60 mg denosumab subcutaneously every 6 months. The results indicate continuous gains in BMD over 6 years, and continued suppression of bone resorption, as shown by bone markers[20]. There were no data on the incidence of fracture.

Long-term safety

There does not appear to be any long-term safety issues with denosumab. The FREEDOM trial group reported that the treatment was well tolerated over 5 years and that there were no cases of subtrochanteric fracture[115]. Similarly, the findings of the 6-year trial indicate that there is no change in the safety profile of denosumab in the long term[20].

Comment

There is evidence for continued increases in BMD with long-term treatment with denosumab for up to 5 years, and bone markers support the long-term suppression of bone resorption with this agent. Neither of the long-term trials reported fracture efficacy. Denosumab does not appear to be associated with any long-term safety issues.

Strontium ranelate

Strontium ranelate has a dual mode of action with opposite effects on bone resorption and formation[116]. This is associated with efficacy in the prevention of vertebral and non-vertebral fracture.

Fracture efficacy between 3 and 5 years

Strontium ranelate has been shown to prevent vertebral, non-vertebral, and hip fracture in postmenopausal osteoporotic women over 3 years in the Spinal Osteoporosis Therapeutic Intervention (SOTI) and Treatment of Peripheral Osteoporosis (TROPOS) trials[117,118], with a good safety profile.

TROPOS is the only preplanned randomized, double-blind, placebo-controlled study focused on non-vertebral fractures in osteoporosis to last for 5 years (Table 1, Figure 1)[13]. TROPOS was completed by 2714 patients ($n = 1384$ strontium ranelate 2 g/day, $n = 1330$ placebo). The fracture efficacy of strontium ranelate was sustained for both vertebral and non-vertebral fracture (including hip in women at high risk according to age and T score)[13]. The primary end point of new non-vertebral osteoporotic fracture occurred in 18.6% of the strontium ranelate group versus 20.9% of the placebo group over 5 years (RR, 0.85, 95% CI, 0.73–0.99). Treatment was associated with similar risk reductions for new major non-vertebral osteoporotic fracture (RR, 0.82, 95% CI, 0.69–0.98) and new vertebral fracture (RR, 0.76, 95% CI, 0.65–0.88), as well as hip fracture in a subset of 1128 patients at higher risk (RR, 0.57, 95% CI, 0.33–0.97)[13]. These reductions in fracture were accompanied by progressive increases in BMD.

A recent preplanned subgroup analysis of 1489 patients in SOTI and TROPOS demonstrated similar efficacy over 5 years was seen in the elderly (aged >80 years at baseline)[119]. Treatment reduced the risk of non-vertebral fracture (RR, 0.73, 95% CI, 0.57–0.95) and vertebral fracture (RR, 0.69, 95% CI, 0.52–0.92).

Fracture efficacy beyond 5 years

The effect of treatment with strontium ranelate has been explored up to 10 years in an open-label extension study, pooling patients from both SOTI and TROPOS. This analysis included 879 patients, who had received continuous treatment with strontium ranelate for 8 years[15] and 233 patients who received strontium ranelate for 10 years[30] (Table 1, Figure 1). These studies suffer the same limitations as the other long-term studies in osteoporosis, with an open-label design and the absence of a placebo control group, precluding any definitive conclusions on the reduction of risk of fracture at 10 years. However, SOTI and TROPOS baseline patients treated for 10 years ($n = 233$) had a profile similar to the whole population with a mean age of 72.0 ± 5.5 years, a mean lumbar spine and femoral neck BMD T-score of -3.30 ± 1.38 and -2.95 ± 0.57, respectively[30]. Over the 10-year period, lumbar BMD increased continuously and significantly ($P < 0.05$ up to year 10) with, at 10 years, a relative change from baseline of $34.5\% \pm 20.2\%$. At the femoral neck and total hip sites, the BMD increased significantly until year 7, with a relative change from baseline of $10.7\% \pm 12.1\%$ and $11.7\% \pm 13.6\%$, respectively, and then remained stable.

The cumulative incidences of new vertebral and non-vertebral fractures (20.6% and 13.7%, respectively) over the 5-year extension were not statistically different ($P = 1.00$ and 0.67, respectively) to the cumulative incidences over the 5 years in the original studies (18.5% and 12.9%, respectively)[30]. To assess the antifracture efficacy of strontium ranelate in the absence of placebo group, the authors searched for a matching population in the placebo group of TROPOS using the 10-year probability of major osteoporotic fracture calculated with FRAX as matching variable. The mean 10-year probability of major osteoporotic fracture, calculated with FRAX, in the 233 patients treated for 10 years with strontium ranelate was 25.8% at the time of their inclusion in the extension study. The incidences of vertebral and non-vertebral fracture observed over the 5 years of TROPOS were significantly higher ($P < 0.05$) in the matching placebo group than those observed in the '10-year' population over the 5-year extension, with a relative risk reduction with strontium ranelate of 35% and 38% for vertebral fractures and non-vertebral fractures, respectively[30].

Long-term safety

Strontium ranelate has a good tolerability profile in the trials to 5 years, and there was no evidence of a change in the long-term trials beyond that[13,15]. The annual incidence of venous thromboembolism in the phase 3 studies was 0.9% versus 0.6% in the placebo group[120]. While RCT evidence may be considered as more reliable than observational data, concerns surrounding this issue have been somewhat allayed by analysis performed within the UK General Practice Research Database[10]. This retrospective cohort study found no difference in the rates of venous thromboembolism in osteoporotic women treated with strontium ranelate ($n = 2408$) or alendronate ($n = 20,084$), versus untreated osteoporotic women ($n = 11,546$)[10]. The same study found that osteoporotic women were more likely to suffer venous thromboembolism than their non-osteoporotic counterparts. Strontium ranelate remained safe and well tolerated over 10 years with no unexpected adverse event[30].

Comment

There is robust evidence for clinical fracture efficacy over 5 years, including in elderly patients, and reports of sustained efficacy on vertebral and non-vertebral fracture over 10 years. The adverse effects profile is also good, with no long-term safety concerns.

Discussion

This review of long-term trials with osteoporosis treatments shows diminishing evidence for sustained fracture effects with increasing duration of the study. There is high-level evidence to 3 years for all the agents covered in this review. Of the studies lasting to 5 years, there is evidence of fracture efficacy for raloxifene in the nonosteoporotic population, for bazedoxifene and lasofoxifene in postmenopausal osteoporosis, for risedronate in a small osteoporotic population, and for denosumab and strontium ranelate in an osteoporotic population. All of the studies beyond 5 years show maintenance of BMD levels in the long term, and, for some agents, indirect evidence for an additional reduction in fracture incidence. In this context, there is uncertainty about the effectiveness of various agents on BMD at different time intervals after baseline. Thus, although most studies document the largest effect during the first year of treatment, many continue to demonstrate effects lasting into the fourth and fifth years of treatment. Another factor may be adjustment for ageing of the populations, though the studies that adjust for age report similar findings to those in which this adjustment is not made. Because the quality of long-term clinical trial data is necessarily lower than in the 3-year phase 3 trials, there is a need for more observational studies to explore the impact of long-term treatment with osteoporosis treatments on fracture incidence.

The occurrence of osteoporotic fracture is known to be linked with an increase in mortality, both for vertebral and non-vertebral fracture. Recent evidence suggested that the osteoporosis treatments may reduce mortality risk in postmenopausal women[121–123]. These effects appear to hold for all the agents tested (bisphosphonates, raloxifene, denosumab, and strontium ranelate) with treatment-related reductions of 11% for total mortality ($P = 0.036$ versus placebo)[121]. These observations underline the importance of managing osteoporosis on a long-term basis.

The occurrence of adverse effects does not appear to be duration dependent, though it should be noted that some events are so rare that it would be difficult to detect an increase. The optimal duration of treatment is uncertain for many agents. Our review suggests that adverse effects are relatively uncommon during the first 5 years of treatment; beyond this time further research is required. A possible exception is atypical subtrochanteric fracture with bisphosphonates, though further research is needed before a definitive link can be established between long-term suppression of bone turnover with bisphosphonates and this rare, but serious, adverse event. This highlights the limitations of using large-scale RCTs to evaluate rates of adverse events, as well as the key role of post-marketing surveillance.

Another important issue is compliance, which is far from optimal in osteoporosis. Long-term clinical studies are performed in generally adherent populations, complicating the extrapolation of the trial findings to daily clinical practice. Indeed, about 50% of patients fail to comply or persist with their treatment within 1 year and less than 60% have adequate compliance at 1 year[124]. Another study suggested that compliance with osteoporosis treatments was between 59% and 81% (medication possession ratios), though compliance data are confounded by the varying length of follow-up in the different studies[125]. Poor compliance (i.e. <80% medication possession ratio) can have a dramatic impact on fracture efficacy and is associated with between 20% and 37% increases in the risk of fracture at various skeletal sites[110,126]. In this context, it is striking that the long-term trials suggested that calcium and vitamin D supplementation was both safe and efficacious in reducing fracture, but that its effect was almost totally compromised by compliance issues. Similar problems have been reported for most of the other osteoporosis treatments[70,110,127]. Compliance can therefore have a considerable impact on the long-term effectiveness of treatment. This is an important point, since the challenge of keeping patients on any treatment beyond 1 year may well be far greater than the challenge of treating for longer than 5 years. In this context, the extent to which cost minimization and patient convenience should be utilized in determining the strategy for use of different treatments remains a controversial policy issue.

In this review on long-term treatments in osteoporosis, we have omitted some agents, which merit a short discussion here. Our aim was to explore the effects of long-term therapies in osteoporosis, implying the necessity of defining a cutoff. We defined 'long-term' as lasting longer than 3 years, since the regulatory requirement for an osteoporosis treatment is that it has been tested in RCTs up to 3 years. This excluded teriparatide and PTH, which are limited to 18 months of treatment. The impact of these treatments over durations of less than 3 years has been widely addressed in the literature[128]. Clearly, these agents remain relevant to the treatment of osteoporosis in the long term since they are favorable in patients with severe osteoporosis. Similarly, calcitonin was not included because it is not widely used, even though there is a 5-year trial of an intranasal formulation of this agent[129]. Treatment with calcitonin (200 IU daily) was associated with a significant reduction in vertebral fracture risk, but there was no dose–response relationship (the reduction in fracture with the highest dose of calcitonin did not reach significance)[130]. Finally, we excluded long-term use of hormone replacement therapy (HRT), which reduces non-vertebral fractures by about 35%[131]. Long-term HRT is also associated with increased risk of coronary heart disease, stroke, thromboembolic events, breast cancer, and cholecystitis[132], and is therefore no longer used for the prevention of osteoporotic fracture.

Conclusion

Even though osteoporosis requires a long-term treatment, which should balance fracture efficacy against the risk of adverse events, robust long-term studies in the field are relatively scarce. We have reviewed the current evidence for long-term efficacy of the osteoporosis treatments including the SERMs, the bisphosphonates, denusomab, and strontium ranelate, as well as supplementation with vitamin D and calcium. Robust data for efficacy and safety are available for up to 5 years, and less than that for some osteoporosis treatments. The studies generally show maintenance of BMD and, for some agents, an additional reduction in fracture incidence. They indicate that adverse effects are generally rare and duration dependent, though their time course requires further study. Currently available evidence allows us to conclude that it is both important and useful to continue to treat osteoporosis in the long term, up to 10 years, to prevent fracture and its deleterious consequences in the elderly. The duration of treatment and the agent selected will depend on individual patient characteristics and, more particularly, the severity of osteoporosis.

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