Long-term antifracture efficacy and safety of antiosteoporotic treatments: the hidden part of the iceberg

J. Bernardino Díaz-López and Jorge B. Cannata-Andía.

Bone and Mineral Research Unit. Hospital Universitario Central de Asturias. Instituto Reina Sofía de Investigación. REDinREN del ISCIII. Universidad de Oviedo. Oviedo, Asturias, Spain.

J. Bernardino Díaz-López: *Associate Professor of Medicine. Hospital Universitario Central de Asturias. Universidad de Oviedo, Spain.*

Jorge B. Cannata-Andía: *Full Professor of Medicine. Hospital Universitario Central de Asturias. Universidad de Oviedo, Spain.*

Running title: Long-term antifracture efficacy.

Key words: Osteoporosis, fragility fractures, Antiosteoporotic drugs, sustained antifracturary efficacy.

Address for correspondence:
Prof. Jorge B. Cannata-Andía
Bone and Mineral Research Unit
Instituto Reina Sofía de Investigación
Hospital Universitario Central de Asturias
C/Julián Clavería, s/n
33006 Oviedo, Asturias
Phone: +34985106137
Fax: +34985106142
E-mail: metoseo@hca.es

Abstract

Long-term antifracture efficacy and safety are the two major goals of any antiosteoporotic treatments. So far, several drugs have proved to be effective and safe during the 2-3 years period of controlled clinical trials but only a few of them have shown bone protection up to 5 years, which is the minimum period in order to assume there is sustained fracture reduction. Raloxifene has shown efficacy in vertebral fracture risk reduction in up to 5 years but no effect in non-vertebral fracture. Risedronate and Alendronate have also shown anti-fracture efficacy in vertebral fracture risk reduction up to 7 and 10 years respectively, but no long-term benefit was observed in non-vertebral fracture.

Strontium ranelate have demonstrated a sustained fracture risk reduction up to 5 years in vertebral and non-vertebral fractures. In addition, preliminary analyses of the 8 years treatment have shown the same trend in vertebral and non-vertebral fracture risk reduction.

In summary, at least 4 drugs have demonstrated a sustained vertebral antifracture efficacy but only strontium ranelate has proved to be long-term efficient in non-vertebral fracture.

Introduction

After beginning therapy, clinicians must confront the question of for how long should therapy continue and how we should evaluate efficacy and safety. Unless there are any obvious safety issues, long-term therapy is generally planned for chronic disorders such as osteoporosis, however how many years "long-term" means has not been clearly defined yet. The second issue is how to evaluate efficacy and safety. For both, well-designed, controlled randomized trials is the answer. When compared to placebo, fractures would determine efficacy outcomes, whereas a negative increment of morbidity would define safety outcomes. For safety, also post-marketing surveillance is valid.

Because of the risks, long-term estrogen replacement therapy is not currently recommended for the management of postmenopausal osteoporosis even though it has been demonstrated that estrogen therapies helps to prevent fractures[1]. The optimal length of use of the other current medications for osteoporosis remains to be established.

For trials, a panel of experts representing ASBMR, NOF and ISCD[2] have provided an answer to for how many years must an agent for osteoporosis be evaluated for its efficacy and safety. They reached consensus that trials may last at least 18 to 24 months with fracture endpoints to test efficacy, and 5 years to properly test safety and to demonstrate a sustained fracture reduction[2].

Nowadays, many drugs have proven to be effective in reducing new osteoporotic fractures in postmenopausal women[3-16] (table 1). Most of these major clinical trials lasted no more than 3 years. In addition, in some of them, such as in the Calcitonin trial, only 46% of the initial participants completed the programmed five-year follow-up, as a result, the grade of evidence was lower and just concerning the 200 IU nasal spray dose, but not the 100 IU and 400 IU sprays[12]. Hence, any assumptions about long-term treatments based on the findings of any type of study, even with 3 years follow-up, should be made with great caution analyzing

the strength of the evidence. Moreover, despite non-vertebral fractures are more prevalent and carry a substantial burden for the patient, most of the osteoporosis treatments that have proven efficacy in reducing the risk of vertebral fracture, have not shown reductions in non-vertebral fracture risk (table 1). Furthermore, information on the clinical efficacy and safety of several active anti-osteoporosis treatments at more than 4-5 years follow-up is limited. Currently, for periods of time of 5 years or more, the only information available is on raloxifene, alendronate, risedronate and strontium ranelate, with different strengths of evidence as we will describe below and they are summarized in tables 2 and 3.

Raloxifene

Raloxifene has shown a vertebral fracture risk reduction after 4 years similar to that after 3 years and it has also shown benefit at 5 years in postmenopausal women not selected on the basis of osteoporosis or increased fracture risk[17,18]. Similar to what it was shown in the pivotal trial, raloxifene had no effect on non-vertebral fracture risk after 5 and 8 years[18,19]. In addition, the absence of effect of raloxifene on non-vertebral fracture was consistent across different subgroups characterized by the presence or absence of risk factors at baseline including a summary of non-vertebral fracture risk score[18]. The effect on bone mineral density (BMD) observed after 3 and 4 years persisted when the drug was administered for 8 years[19]. However, as it was seen with estrogen replacement therapy, a sharp drop in BMD occurred upon raloxifene discontinuation[17]. The long-term safety profile is also similar to that observed in the first 3 yeas, with an increase in the risk of deep vein thrombosis, and a significant decrease in the incidence of invasive estrogen-receptor positive breast cancer[20-21]. As opposed to the findings relating to estrogen replacement therapy, no evidence of coronary or cerebrovascular events has been found in postmenopausal osteoporotic women at relatively low risk of cardiovascular events[21].

Bisphosphonates

Long-term bone protection provided by alendronate and risedronate has been examined in a series of extensions of previously reported pivotal clinical trials[22-26]. These studies show that the anti-fracture efficacy is maintained over time, for up to 7 years with risedronate and up to 10 years with alendronate[23,26]. The rates for non-vertebral fractures did not differ significantly between the groups who continued to receive alendronate or risedronate and those receiving placebo[23,26]. Between the 5th and the 10th year of treatment, alendronate only reduced the incidence of clinical vertebral fractures but not the morphometric vertebral fractures compared to placebo[26]. In the case of risedronate, the study was too small to detect differences in non-vertebral fractures on years 4 and 5 (table 3). However, an intention-to-treat analysis including 689 patients found a significant risk reduction in non-vertebral fractures from year 1 to year 5 (HR 0,63, 95 CI 0,42 to 0,94)[22]. Nevertheless, despite some positive results from non-pivotal trials, definitive evidence for a non-vertebral fracture benefit with risedronate or alendronate up to 5 years of treatment is lacking. However, it is important to note that non-vertebral fracture risk remains reduced. after discontinuation of both alendronate or risedronate[23,26,27].

Regarding bone mass, alendronate and risedronate maintained BMD gains for 10 and 7 years, respectively[23,25]. Cumulative increases in BMD at the hip and spine, and reductions in bone turnover markers (BTM) were greater for women who kept receiving these aminobisphosphonates compared with those who had discontinued it[23-26]. However, in women discontinuing alendronate or risedronate who then received placebo in the extension studies, BMD remained high, and the BTM reduction was greater than values at baseline[23-25]. These results, together with those described for fractures, suggest that for many women, discontinuation of these aminobisphosphonates for 1 or more years does not appear to significantly increase fracture risk. As bisphosphonates feature a long residence time in bone,

and concerns about it have emerged, the concept of "drug holidays" has been coined for this kind of drugs[28].

"Drug holidays" time would vary depending on the type of aminobisphosphonate. With alendronate, which appears to have a longer skeletal retention time than risedronate[29], the drug holiday period could be longer, up to 5 years, especially for women who were compliant for prolonged periods of time. Although we need more data before issuing any definitive recommendations regarding the optimal length of drug holiday for alendronate and risedronate, such strategies deserve consideration, especially if we take into account the recent unusual fracture cases associated with long-term alendronate treatment[30-32].

Overall, alendronate and risedronate were well tolerated during the 10 and 7 years of the extension studies[22-26]. No new safety concerns were observed during the extension studies of alendronate and risedronate when compared to the safety observations gathered during the first 3 years of the pivotal studies. Nevertheless, there is growing concern that long-term suppression of bone turnover with bisphosphonates may eventually lead to an accumulation of fatigue-induced damage and that it may be associated with a new form of insufficiency fracture of the femur[30-32].

In the last years, there have been reports on the association of subthrochanteric and diaphyseal femur fractures with alendronate long-term treatments[30-32]. However, and although we would advice to be cautious, according to the national observational register-based studies and recent case-control studies, this unusual femur fracture, if it does happen, is very unlikely to be associated with bisphosphonates[33,34]. The same comment is valid for the osteonecrosis of the jaw another potential side effect related to bisphosphonates, clearly associated with very high intravenous doses of aminobisphosphonates used in cancer patients, meanwhile the incidence or prevalence of osteonecrosis of the jaw in patients taking bisphosphonates for osteoporosis appears to be comparable to that in the general population[35,36].

The report describing a significant increase in the risk of serious atrial-fibrillation associated with once-yearly infusions of intravenous zoledronic acid in the Horizon trial[10] prompted an investigation on the possibility of an increased risk of atrial-fibrillation with other bisphosphonates used for osteoporosis in postmenopausal women. The first report reviewing the FIT trial did show a trend towards an increased risk of serious adverse events with alendronate that resemble the pattern observed in the Horizon study[37], but there was no increase in atrial-fibrillation . A later, population-based case-control study showed that the use of alendronate was never associated with an increased risk of incident atrial-fibrillation in clinical practice[38]. Two more recent studies of large databases analysed the former observation, and failed to find any links between bisphosphonate therapy and atrial-fibrillation [39,40].

Strontium ranelate

The efficacy of strontium ranelate has been assessed in 2 multicentre, randomized, double-blind, placebo-controlled trials, originally planned for 5 years[13,14]. Five-year data are now available from the Spinal Osteoporosis Therapeutic Intervention (SOTI), including 4 years against placebo and from the TReatment Of Peripheral Osteoporosis Study (TROPOS) including 5 years against placebo[41,42]. Furthermore, since the acquisition procedures and central readings were the same, data could be pooled in order to obtain a large database in which subanalyses could be conducted to appropriately assess the determinants of efficacy and safety for strontium ranelate[43-45].

The main result of these pre-planned analyses is that long-term treatment (4 and 5 years) with strontium ranelate significantly reduced not only the risk of vertebral fractures but also the risk of non-vertebral fractures[41,42]. Regarding the latter, it is important to note that strontium ranelate is the only antiosteoporotic treatment that have shown a long-term efficacy

in non-vertebral fractures compared to placebo. Moreover, in a post-hoc analysis, there was a 43% decrease in the risk of hip fracture in a subset of 1,128 patients defined as a group with high risk of fractures[41]. The anti-fracture efficacy of strontium ranelate has been documented across a wide range of patient profiles, including osteopenia and very elderly women[43-45]. Besides this, the reduction in fractures came together with a significant improvement in quality of life and an increase in the number of patients free of back pain[41,42].

Recently, the extension of the previous pivotal studies up to 8 years of follow-up has been presented[46] (figure 1). This long-term results demonstrated that strontium ranelate maintain its efficacy on vertebral and non-vertebral fractures (13.7% and 12%, respectively) at 5 and 8 years, and the incidence of fractures was similar to that observed in SOTI and TROPOS at 3 years (14.9% and 11.2%, respectively)[46]. The reduction in fracture risk was associated with a progressive BMD increase at the lumbar and hip regions throughout all the treatment period[41,42], showing a continuous and significant increase in BMD over 8 years at lumbar spine and over 7 years at femoral neck[46].

After treatment withdrawal, patients who switched to placebo at 4 years experienced a significant reduction in BMD, by 3.2% and 2.5% at lumbar spine and hip, respectively[41]. This decrease in BMD in the year following the treatment seems to have the same slope as the one observed for annual increase in BMD during the first year of treatment. Following treatment withdrawal, the BTM results were also in agreement with the BMD. According to the dual mode of action of the drug, a significant decrease in bone alkaline phosphatase and increase of serum C-telopeptide cross-link of type 1 collagen was observed. These changes were already detected 3 months after treatment discontinuation suggesting a relatively rapid release of strontium from bone[41,42].

In the context of clinical trials, safety was good, and the most common adverse events related to strontium ranelate were nausea and diarrhoea during the first 3 months[41-43]. A slight

increase in the annual incidence of venous thromboembolism (0.9% vs. 0.6%) was observed at 3 yrs, and remained unchanged from the third year on, without any known underlying potential mechanism[41-43]. During post-marketing surveillance, isolated cases of hypersensitivity syndrome or DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) have been reported. The clinical manifestations typically occur within 2–6 weeks after initiating therapy and in most cases are resolved upon discontinuation. This syndrome has been very rarely reported (16/570 000 patient-years)[47]. However, due to the potential fatal outcome linked to this syndrome, the treatment should be discontinued immediately and permanently in case of skin rash and treatment and medical follow-up should be initiated.

Summary

Therefore, so far we have many pharmacological agents available for the effective long-term reduction of osteoporotic fractures. It should be also noted that for most other diseases, the equivalence of acute and chronic treatment is implicit; osteoporosis is, however, a rare example of a chronic disease in which controlled studies have been extended up to 10 years. The drugs with longer time of controlled follow-ups are alendronate (10 years), strontium ranelate (8 years), risedronate (7 years) and raloxifene (up to 8 years). All of them maintained up to 5 years the antifracture efficacy in vertebral fracture but not in non-vertebral fracture, except strontium ranelate that has proven to be long-term efficient for both vertebral and non-vertebral fractures. This profile together with its wide spectrum of efficacy allows the use of strontium ranelate as a first-line intervention for long-term treatment in postmenopausal women with osteoporosis.

Finally, two important practical remarks, firstly we have to be aware that all the controlled studies with active antiosteoporotic agents where supplemented with calcium and vitamin D, thus an adequate nutrition and optimal vitamin D repletion seems to be always

necessary to maximize the response of all the antiosteoporotic drugs[48]. Secondly, another crucial aspect to be kept in mind for any long-term treatment is the adherence to the prescribed intervention[49], this important topic will be addressed in the next chapter.

References

1. *Cauley JA, Robbins J, Chen Z, et al. Effects of Estrogen Plus Progestin on Risk of Fracture and Bone Mineral Density: The Women's Health Initiative Randomized Trial. JAMA. 2003 October 1, 2003;290(13):1729-38.*
2. *Silverman SL, Cummings SR, Watts NB. Recommendations for the Clinical Evaluation of Agents for Treatment of Osteoporosis: Consensus of an Expert Panel Representing the American Society for Bone and Mineral Research (ASBMR), the International Society for Clinical Densitometry (ISCD), and the National Osteoporosis Foundation (NOF). J Bone Miner Res 2008; 23: 159-165.*
3. *Liberman UA, Weiss SR, Bröll J et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group. N Engl J Med 1995; 333:1437– 1443.*
4. *Black DM, Cummings SR, Karpf DB, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet 1996; 348:1535–1541.*
5. *Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA 1998; 280: 2077–2082.*
6. *Harris ST, Watts NB, Genant HK et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. JAMA1999; 282:1344–1352.*
7. *Reginster J, Minne HW, Sorensen OH, et al. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. Osteoporos Int 2000; 11:83–91.*
8. *McClung MR, Geusens P, Miller PD et al. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. N Engl J Med 2001; 344: 333–340.*
9. *Chesnut CH III, Skag A, Christiansen C et al. Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. J Bone Miner Res 2004; 19:1241–1249.*
10. *Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med 2007; 356:1809–1822.*
11. *Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene. Results from a 3-year randomized clinical trial. JAMA1999; 282:637–645.*
12. *Chesnut CH 3rd, Silverman S, Andriano K et al. A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the prevent recurrence of osteoporotic fractures study. PROOF Study Group. Am J Med 2000; 109:267–276.*
13. *Meunier PJ, Roux C, Seeman E, et al. The effects of strontium ranelate on the risk of vertebral fracture in women withpostmenopausal osteoporosis. New Engl J Med 2004; 350:459–468.*

14. *Reginster JY, Seeman E, De Vernejoul MC, et al. Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: Treatment of Peripheral Osteoporosis (TROPOS) study. J Clin Endocrinol Metab 2005; 90:2816–2822.*

15. *Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1–34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med; 2001; 344:1434–1441.*

16. *Greenspan SL, Bone HG, Ettinger MP, et al. Effect of Recombinant Human Parathyroid Hormone (1-84) on Vertebral Fracture and Bone Mineral Density in Postmenopausal Women with Osteoporosis: A Randomized. Ann Intern Med 2007; 146: 326-339.*

17. *Delmas PD, Ensrud KE, Adachi JD, et al. Efficacy of Raloxifene on Vertebral Fracture Risk Reduction in Postmenopausal Women with Osteoporosis: Four-Year Results from a Randomized Clinical Trial. J Clin Endocrinol Metab 2002; 87: 3609–3617.*

18. *Ensrud KE, Stock JL, Barrett-Connor E, et al. Effects of raloxifene on fracture risk in postmenopausal women: the Raloxifene Use for the Heart Trial. J Bone Miner Res. 2008; 23: 112-120.*

19. *Siris, ES, Harris ST, Eastell R, et al. Skeletal effects of raloxifene after 8 years: results from the continuing outcomes relevant to Evista (CORE) study. J Bone Miner Res 2005; 20: 1514-1524.*

20. *Barrett-Connor E, Mosca L, Collins P, et al. Effects of Raloxifene on Cardiovascular Events and Breast Cancer in Postmenopausal Women. N Engl J Med 2006; 355: 125-137.*

21. *Ensrud K, Genazzani AR, Geiger MJ et al. Effect of raloxifene on cardiovascular adverse events in postmenopausal women with osteoporosis. Am J Cardiol 2006; 97: 520-527.*

22. *Sörensen OH, Crawford GM, Mulder H, et al. Long-term efficacy of risedronate: a 5-year placebo-controlled clinical experience. Bone.2003;32:120-126.*

23. *Mellstrom DD, Sorensen OH, Goemaere S, Roux C, Johnson TD, Chines AA. Seven Years of Treatment with Risedronate in Women with Postmenopausal Osteoporosis. Calcif Tissue Int. Calcif Tissue Int. 2004; 75: 462-468.*

24. *Ensrud KE, Barrett-Connor EL, Schwartz A, et al. Fracture Intervention Trial Long-Term Extension Research Group. Randomized trial of effect of alendronate continuation versus discontinuation in women with low BMD: results from the Fracture Intervention Trial long-term extension. J Bone Miner Res 2004;19:1259-1269.*

25. *Bone HG, Hosking D, Devogelaer JP, et al. Alendronate Phase III Osteoporosis Treatment Study Group. Ten years' experience with alendronate for osteoporosis in postmenopausal women. N Engl J Med. 2004; 350:1189-1199.*

26. *Black DM, Schwartz AV, Ensrud KE, et al, for the FLEX Research Group. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX). A randomized trial. JAMA. 2006;296:2927-2938.*

27. *Watts NB, Chines A, Olszynski WP, et al. Fracture risk remains reduced one year after discontinuation of risedronate. Osteoporos Int 2008; 19:365–372.*

28. *Curtis JR, Westfall AO, Cheng H, Delzell E, Saag KG. Risk of hip fracture after bisphosphonate discontinuation:implications for a drug holiday Osteoporos Int 2008;19:1613-1620.*

29. *Nancollas GH, Tang R, Phipps RJ, et al. Novel insights into actions of bisphosphonates on bone: differences in interactions with hydroxyapatite. Bone. 2006;38: 617-627.*

30. *Odvina CV, Zerwekh JE, Rao DS, Maalouf N, Gottschalk FA, Pak CYC. Severely Suppressed Bone Turnover: A Potential Complication of Alendronate Therapy. J Clin Endocrinol Metab 2005;90(3):1294-1301.*

31. *Armamento-Villareal R, Napoli N, Panwar V, Novack D. Suppressed Bone Turnover during Alendronate Therapy for High-Turnover Osteoporosis. N Engl J Med 2006; 355: 2048-2050.*

32. *Goh SK, Yang KY, Koh JSB, et al. Subtrochanteric insufficiency fractures in patients on alendronate therapy: A caution. J Bone Joint Surg Br 2007; 89: 349-353.*

33. *Abrahamsen B, Eiken P, Eastell R. Subtrochanteric and diaphyseal femur fractures in patients treated with alendronate: a register-based national cohort study. J Bone Miner Res. 2009; 24: 1095-1102.*

34. *Lenart BA, Neviaser AS, Lyman S, et al. Association of low-energy femoral fractures with prolonged bisphosphonate use: a case control study. Osteoporos Int. 2008 Dec 9. [Epub ahead of print]*

35. *Rizzoli R, Burlet N, Cahall D, et al. Osteonecrosis of the jaw and bisphosphonate treatment for osteoporosis. Bone. 2008; 42: 841-7.*

36. *Khan AA, Sandor GK, Dore E, et al. Bisphosphonate associated osteonecrosis of the jaw. J Rheumatol 2009; 36: 478-490.*

37. *Cummings SR, Schwartz AV, Black DM. Alendronate and Atrial Fibrillation. N Engl J Med 2007; 356:1895-1896.*

38. *Heckbert SR, Li G, Cummings SR, Smith NL, Psaty BM. Use of alendronate and risk of incident atrial fibrillation in women. Arch Intern Med. 2008; 168: 826-831.*

39. *Sorensen HT, Christensen S, Mehnert F, et al. Use of bisphosphonates among women and risk of atrial fibrillation and flutter: population based case-control study. Bmj 2008; 336: 813-816.*

40. *Bunch TJ, Anderson JL, May HT, et al. Relation of bisphosphonate therapies and risk of developing atrial fibrillation. Am J Cardiol. 2009;103:824-828.*

41. *Reginster JY, Felsenberg D, Boonen S, et al. Effects of long-term strontium ranelate treatment on the risk of non-vertebral and vertebral fractures in postmenopausal osteoporosis: results of a 5-year, randomized, placebo-controlled trial. Arthritis and Rheumatism 2008; 58(6):1687–1695.*

42. *Meunier PJ, Roux C, Ortolani S, et al. Effects of long-term strontium ranelate treatment on vertebral fracture risk in postmenopausal women with osteoporosis. Osteoporos Int. 2009 Jan 20. [Epub ahead of print].*

43. *Roux C, Reginster JY, Fechtenbaum J, et al. Vertebral fracture risk reduction with strontium ranelate in women with postmenopausal osteoporosis is independent of baseline risk factors. J Bone Miner Res 2006; 21: 536-542.*

44. *Roux C, Fechtenbaum J, Kolta S, Isaia G, Andia JB, Devogelaer JP. Strontium ranelate reduces the risk of vertebral fracture in young postmenopausal women with severe osteoporosis. Ann Rheum Dis 2008;67:1736-1738.*

45. *Seeman E, Vellas B, Benhamou C, Aquino JP, Semler J, Kaufman JM, et al. Strontium ranelate reduces the risk of vertebral and nonvertebral fractures in women eighty years of age and older. J Bone Miner Res 2006; 21: 1113-1120.*

46. *Reginster JY, Sawicki A, Roces-Varela A, Fardellone P, Roberts A. Strontium ranelate 8 years efficacy on vertebral and nonvertebral fractures in postmenopausal osteoporotic women. Osteoporos Int 2008; 19(Suppl.1): S131-S132 (Abstract P311).*

47. *European Public Assessment Reports(EPARs) for authorised medicinal products for human use. Protelos. Press Release (2007). Available at: http://www.emea.europa.eu/humandocs/PDFs/EPAR/protelos/PressRelease_Protelos_41745807en.pdf.*

48. *Adami S, Giannini S, Bianchi G, et al. Vitamin D status and response to treatment in post-menopausal osteoporosis. Osteoporos Int 2009; 20: 239-244.*

49. *Solomon DH, Avorn J, Katz JN, et al. Compliance with osteoporosis medications. Arch Intern Med 2005; 165: 2414-2419.*

Table 1.- Pivotal trials for osteoporotic fracture risk reduction in postmenopausal women.

Drug / Trial	Follow-up	Fracture Risk Reduction Vertebral / Non-vertebral
Alendronate &		YES / YES
Liberman [3]	0-3 years	Yes / -
FIT VF [4]	0-3 years	Yes / - *
FIT w/o VF [5]	0-4 years	Yes / -
Risedronate &		YES / YES
VERT-MN [6]	0-3 years	Yes / - *
VERT-NA [7]	0-3 years	Yes / Yes
HIP [8]	0-3 years	- / Yes
Ibandronate		YES / -
BONE [9]	0-3 years	
Zoledronic acid		YES / YES
HORIZON [10]	0-3 years	
Raloxifene		YES / -
MORE [11]	0-3 years	
Calcitonin		YES**/ -
PROOF [12]	0-5 years #	
Strontium Ranelate &		YES / YES
SOTI [13]	0-3 years	Yes / -
TROPOS [14]	0-3 years	Yes / Yes
Teriparatide		YES / YES
FPT [15]	21 months	
1-84 PTH		YES / -
TOP [16]	18 months	

& Efficacy observed by metanalysis of the major clinical trials; *nearly of significance #high rate of drop-out; **lower level of evidence and only with 200 UI.

Table 2.- Study and patients characteristics of at least 5 years placebo-controlled trials for osteoporotic fracture risk.

Treatment	**Brief Study Description**	**Mean Age** Placebo - Treatment	**Prior Vertebral Fracture**
Raloxifene[18]	Postmenopausal women (N=10101) with CHD* or multiple risk factors for CHD. Raloxifene 60 mg/day. Fractures as secondary outcome. Mean time follow-up 5, 6 years.	67,5 – 67,5 years	Not determined
Risedronate[22]	Extension study from year 3 to year 5 in postmenopausal women (N=265) with established osteoporosis (1/3 of VERT study), 220 women completed the additional 2 years with Risedronate 5 mg/day.	72,6 – 72,4 years	100 %
Alendronate[26]	Extension study in posmenopausal women (N=1099) (1/3 of FIT study), with a mean of 5 years prior alendronate treatment, randomized to placebo, alendronate 5 mg/d or 10 mg/d for 5 years.	73,7 – 72,8 years	34 %
Strontium Ranelate[41]	Postmenopausal women (N=2714), 57% completed five years of the randomized TROPOS study whit strontium ranelate 2gr/day.	76,8 – 76,7 years	33,6 %

*CHD = coronary heart disease

Table 3.- Vertebral and Non-Vertebral Fracture incidence by treatment (trials described in table 2)

Treatment	**Type of Fracture**	**Incidence (%)** **Placebo - Treatment**	**Treatment Effect** **RR (95% CI*)**
Raloxifene[18]	Clinical Vertebral fracture	1,9 – 1,3	0,65 (0,47- 0,89)
	Non-vertebral fracture	8,7 – 8,5	0,96 (0,84- 1,10)
Risedronate[22]	Vertebral fracture	28,2 – 13,8	0,41 (0,21- 0,81)
	Non-vertebral fracture	8,5 – 5,2	0,59 (0,22- 1,57)
Alendronate[26]	Clinical Vertebral fracture	5,3 – 2,4	0,45 (0,24- 0,85)
	Non-vertebral fracture	19,0 – 18,9	1,00 (0,76- 1,32)
Strontium Ranelate[41]	Vertebral fracture	24,9 – 20,8	0,76 (0,65- 0,88)
	Non-vertebral fracture	20,9 – 18,6	0,85 (0,73- 0,99)

*CI: Confidence Interval

Figure 1. Reduction in the risk of A)Vertebral and B)Non-vertebral fractures with strontium ranelate after 8 years of follow-up (46).