



ELSEVIER

Available online at www.sciencedirect.com

SCIENCE @ DIRECT®

Maturitas 48 (2004) 179–192

MATURITAS

THE EUROPEAN
MENOPAUSE
JOURNAL

www.elsevier.com/locate/maturitas

Review

Postmenopausal osteoporosis and alendronate

Faustino R. Pérez-López*

*Department of Obstetrics and Gynaecology, University of Zaragoza Faculty of Medicine,
Hospital Clínico de Zaragoza, San Juan Bosco 15, Zaragoza 50010, Spain*

Received 15 May 2003; received in revised form 1 December 2003; accepted 9 December 2003

Abstract

Osteoporosis is a systemic metabolic disorder associated with a decreased bone mass and resistance. Bisphosphonates suppress bone resorption and bone turnover by a mechanism that depends on their structure. They are characterized by low gastrointestinal absorption. In postmenopausal women, alendronate (ALN) reduces bone resorption markers and increases bone mineral density (BMD) in the lumbar spine, femoral neck, and total body. Individuals receiving ALN have been studied for up to 10 years with an apparent linear increase in BMD over that time period estimated at 13.7% at the lumbar spine. Treatment with ALN reduced the risk of both vertebral and non-vertebral fractures, including hip fractures, in postmenopausal women with osteoporosis. Direct comparisons of the results obtained with different antiresorptive agents is difficult, because the designs of the respective studies, populations and other factors. However, the meta-analysis of available publications seems to indicate that ALN reduces the relative risk of vertebral fractures in a greater proportion than any other agent. Furthermore, ALN prevents the reduction in BMD after hormone replacement therapy discontinuation.

© 2004 Elsevier Ireland Ltd. All rights reserved.

Keywords: Postmenopausal osteoporosis; Alendronate; Fracture; Bisphosphonates; Antiresorptives; Bone mineral density; Bone mass; Bone quality

1. Introduction

Osteoporosis is a multifactorial systemic metabolic disorder mainly characterized by a decreased bone mass and resistance. However, osteoporosis has also been conceptualized as a risk factor, and described as “disease mongering” [1,2] that has created a hot debate concerning the diagnosis and the treatment [3,4]. Its etiology involves genetic, environmental, hormonal and nutritional factors. Identification of the genes responsible for osteoporosis will allow for future

identification of clinical variants with a greater or lesser rate of bone loss, and will make it possible to design strategies adapted to each individual patient and disease risk [5,6].

Bone fractures related to osteoporosis, particularly vertebral and hip fractures, cause significant suffering and are associated with high mortality and decreased quality of life [7]. The prevalence of fractures related to postmenopausal osteoporosis is very high; indeed, osteoporotic fractures are more frequent than the sum of cases of myocardial infarction, breast cancer and stroke [8–10]. In the specific case of gynecological practice, the risk of a woman suffering a fracture related to osteoporosis is greater than the sum of the

* E-mail address: gine@posta.unizar.es (F.R. Pérez-López).

risk of breast and genital cancer. Moreover, 20% of all women experiencing one of these fracture will suffer another within a year [11]. Osteoporotic fractures are three times more common in the vertebrae than in the hip. In addition to fractures, osteoporosis causes deformity and height loss, pain highly refractory to treatment, reduced physical activity, respiratory complications, limited social activities, dependency upon other persons, etc. This disheartening prospect irreversibly impairs health and generates enormous health care expenses. Apart from clinical impairment and worsened quality of life, it should be remembered that the financial cost of fully established clinical conditions is substantially greater than the cost associated with the application of effective preventive measures.

2. Screening and identification of osteoporosis

The WHO defines osteoporosis as the presence of a bone mineral density (BMD), the most widely used surrogate parameter, more than 2.5 standard deviations (S.D.) below the maximum mean densitometric value in young women [12]. However, the risk of fracture does not begin at this arbitrary value, but is a variable inversely related to BMD. For this reason, the cut-off point for the diagnosis and treatment of osteoporosis is highly controversial.

The US National Osteoporosis Foundation recommends starting treatment to prevent fractures in postmenopausal women with a densitometric *T* score of under two in the absence of risk factors, and with a *T* score of under 1.5 if risk factors exist [13]. The measures to be taken depend on patient characteristics, i.e. on the risk of future fracture regardless of age, the clinical evidence in each case, and the scientific results obtained with drugs that reduce the occurrence of bone fractures. It should be noted that during the process of bone mass loss, in general, all skeletal sites are at risk of fracture; it is therefore desirable to use treatments covering the whole skeletal structure—both vertebral and otherwise. In this setting, bisphosphonates are the antiresorptive drugs which have been shown in randomized studies to prevent fractures. By contrast, only partial or incomplete evidence exists for hormonal therapies, calcium and Vitamin D, calcitonin or fluoride therapy.

Screening for osteoporosis should identify perimenopausal women at risk before the start of rapid bone mass loss. Screening and identification of women at risk of osteoporosis is not easy, and no simple methods are available. The US National Osteoporosis Foundation recommends the measurement of BMD in all women aged 65 or over, as well as in younger women with one or more risk factors [13]. While some physicians screen all women, others perform no screening at all, due to the high cost of densitometry, the reference technique for detecting a decreased BMD. Weinstein and Ullery [14] administered a questionnaire with the potential risk factors to 1610 women (mean age: 62 years) who were then subjected to dual photon densitometry of the spine, hip and femoral neck. Osteoporosis was detected in 35.3% of the women in one or more of the sites evaluated. The only variable that predicted the existence of osteoporosis was the absence of exposure to estrogens as oral contraceptives or hormone replacement therapy (HRT). The independent variables with predictive value were advanced age, reduced body weight, and years since menopause. In the study, authors concluded that many of the accepted risk factors are not reliable to establish who should participate in a screening program. Based on the confidence limits, screening can be recommended in women over age 65 with a body weight of under 140 pounds (57 kg) at the time of menopause, or who have not used estrogens for at least 6 months.

Kovacs [15] has evaluated four guidelines for taking the decision to perform densitometry: *simple calculated osteoporosis risk estimation* (SCORE) [16]; *osteoporosis risk assessment instrument* (ORAI) [17]; *age, body size, no estrogen* (ABONE) [14]; and a *body weight* of under 70 kg [18], to determine how they fit the recommendations of the US National Osteoporosis Foundation. The SCORE and ORAI guidelines offer the best discriminatory capacity for all BMD thresholds. For detecting BMD with a *T* score of under 2.0 standard deviations (the threshold for pharmacological treatment), the sensitivity was 93.7% for the US National Osteoporosis Foundation guideline, 97.5% for SCORE, 94.2% for ORAI, 79.1% for ABONE, and 79.6% for the weight criterion.

The US Preventive Service Task Force stated that screening 731 women aged 65–69 years would prevent one hip fracture if those with indications for treatment

took it, and screening 248 women would prevent one vertebral fracture. The benefits of screening are relatively small in women under the age of 65 years, unless they have other risk factors for osteoporosis [19].

3. Objectives of prevention and treatment of osteoporosis

Success in the prevention and treatment of osteopenia and osteoporosis requires the achievement of a number of pathophysiological objectives leading to the prevention of fractures [20–23]. The first effect of a treatment becomes evident as changes in the different bone metabolic markers. These biochemical changes affect the markers of bone resorption and formation. An increase in bone turnover causes an imbalance between bone resorption and formation which is reflected as a decreased BMD, a loss of connective trabeculation and a reduction in mineralization [24].

The second change refers to a gain in BMD, measurable by densitometry, as a result of tissue reconstruction by the bone metabolic unit, and which occurs after months of treatment. It has been claimed that the greater the increase in BMD, the greater bone resistance. However, increases in BMD are associated with variable changes in bone microarchitecture, so that different treatments induce different densitometric and microarchitectural responses which correlate to an increased or reduced risk of bone fracture. In other words, although BMD is a significant determinant of bone resistance and of the risk of fracture, the relationship is not linear, and small reductions in BMD are associated to disproportionately large increases in fracture risk [25–27], suggesting that some other associated factor exists which increases fracture risk in a complementary manner to bone mass. Apart from these considerations, however, reduced BMD levels warrant treatment to improve bone resistance.

The objective of treatment is to reduce the incidence of bone fractures and the desirable clinical benefit. There are two meta-analyses showing the existence of a significant association between increased BMD in the lumbar spine and hip and the risk of new radiographic vertebral fractures during treatment with antiresorptive drugs [20,28]. Different potential mechanisms of action of antiresorptive drugs exist, particularly on the risk of vertebral fracture: (1)

reduction in the number of active resorption units; (2) inhibition of excessive resorption allows bone to respond to the mechanical demands; (3) reduced bone turnover would prevent trabecular plate perforation and trabecular loss; and (4) reduced bone turnover would allow for complete mineralization [29].

Bone turnover is approximately 30% per year in trabecular bone, i.e. about 10-fold higher than in cortical bone. Therefore, changes in bone turnover and in BMD in cortical bone would be better indicators of the risk of non-vertebral fractures during antiresorptive treatment [28]. Pharmacological agents which induce few changes in the biochemical markers of bone turnover and few changes in BMD are of scant efficacy for preventing non-vertebral fractures. The message for the clinician is that antiresorptive agents inducing the greatest increases in BMD and maximum reductions in biochemical markers compared to placebo should be used.

In this context, the available scientific evidence varies for the different treatment modalities, though the results of greatest value based on design and methodology, randomization and follow-up refer to alendronate (meta-analysis of all treatments available for osteoporosis following the methodology of Cochrane) [30]. Moreover, direct, randomized comparisons of alendronate versus different antiresorptive drugs in postmenopausal osteoporosis have become available very recently.

4. Pharmacology of bisphosphonates and mechanism of action of alendronate

The bisphosphonates are the most potent antiresorptive drugs available for the treatment of postmenopausal osteoporosis. They all share the pyrophosphate structure, which characterizes the pharmacological group. The bisphosphonates are structural analogs of pyrophosphates with specific activity upon bone, thanks to their potent chemical affinity for hydroxyapatite, the main organic component of bone. Bisphosphonates were formerly classified according to the chemical group added to the base pyrophosphoric nucleus at its R2 side chain [31,32]. Accordingly, bisphosphonates were classified in the early 1990s into three generations; alkyl derivatives constituted the first generation of drugs, of which etidronate is representative.

The second generation included the aminobisphosphonates with a terminal amino group (e.g., alendronate and pamidronate), while the third generation was characterized by having a cyclic side chain, as in the case of risedronate [32]. Currently, the tendency is to classify the bisphosphonates according to their biochemical mechanism of action: nitrogenated bisphosphonates or aminobisphosphonates (acting through the mevalonate biochemical pathway) and non-nitrogenated bisphosphonates (which act through ATPases) [33]. The drugs most widely used in clinical practice are alendronate and risedronate, while ibandronate and zoledronate are currently undergoing development.

All bisphosphonates are characterized by low gastrointestinal absorption (approximately 1% of the administered dose), which can be totally neutralized if the drug is administered with any type of food. Uptake by bone is quite constant, with a half-life of the incorporated drug of over 10 years. At high doses they interfere with the mineralization process, causing osteomalacia. However, the resorption/mineralization ratio of the aminobisphosphonates is so great that they do not interfere with this process, as a result of which the therapeutic dose is about 1/100 the dose that causes osteomalacia.

The bisphosphonates modify calcium metabolism. Bone calcium resorption decreases and intestinal absorption increases, as a result of which the calcium balance is positive. These drugs reduce the differentiation and recruitment of osteoclast precursors formed from the hemopoietic stem cells. At the same time, they increase osteoclast apoptosis, partly by caspase activation. The end result is, therefore, a marked reduction in the number of these cells. The third action of this group of drugs is on osteocytes (the cells responsible for skeletal resistance to mechanical loading), whose half-life is prolonged (i.e. premature apoptosis such as that seen in osteoporosis is avoided).

Alendronate sodium (4-amino-1-hydroxybutylidene-1,1-bisphosphonate) is a bisphosphonate which is poorly absorbed following oral administration, and the assimilated fraction is rapidly bound to the bone remodeling units or is excreted in urine as the unchanged molecule [34]. The drug does not cross the cell membranes of other tissues, and therefore, has no extra-skeletal effects, i.e. the effects are limited to the bone cells [35]. As with all bisphosphonates, alendronate firmly binds to bone minerals,

preventing osteoclast resorption by inhibition of the mevalonate–cholesterol pathway. Moreover, the drug possibly acts upon the osteoblasts, stimulating the synthesis of growth factors and inhibiting osteocyte apoptosis [36].

Experimental studies in animals suggest that bisphosphonates can also have chondroprotective effects upon cartilage. This possibility has recently been confirmed in humans in a controlled, randomized study involving alendronate [37]. Type II collagen is almost exclusively located in cartilage, where it constitutes the main structural component, and is excreted in urine as type II collagen-C-telopeptide (CTX-II). In healthy menopausal women, treatment for 3 years with 20 mg of alendronate reduces this peptide by half, a change which becomes evident after 3 months of administration of the drug and persists almost without variation for the remaining period of time. When treatment is discontinued, the CTX-II levels return to the baseline values. These results suggest that, in addition to its effects upon bone metabolism, alendronate also probably inhibits cartilage destruction.

5. Effects of alendronate upon biochemical parameters and densitometry in postmenopausal osteoporosis

Alendronate sodium has been extensively evaluated in clinical trials for over a decade in aspects ranging from the metabolic, densitometric and histomorphologic changes and clinical tolerability to results regarding the incidence of all types of fractures. The patient age range is also very wide (55–81 years), and the bone status has varied from densitometric *T* scores of between –1.6 and –4, and with and without a history of fracture. The scientific evidence is, therefore, comprehensive and will be mentioned here of those data which may prove clarifying for the clinical.

Treatment with alendronate, both daily and weekly, with calcium and Vitamin D supplements, reduces bone resorption markers after 1 month of administration to levels characteristic of the premenopausal phase, while bone formation marker levels decrease after 3 months of treatment [37,38]. Thus, the biochemical changes are both rapid and sustained during treatment with alendronate, and bone markers are

maintained within the levels characteristic of premenopausal women [39].

Alendronate rapidly increases bone mass in the lumbar spine and hip both with daily treatment and with weekly administration. BMD increases are significant compared to baseline values after 6 months of therapy. After 24 months, a 6.8% increase is recorded for weekly alendronate treatment, versus 7.4% for daily administration [40]. Part of the increase in BMD is due to secondary mineralization, which shows levels typical of premenopausal status [29].

Long-term treatment with alendronate has a sustained efficacy, with no evident plateau effect [39]. In a study started in the early 1990s, a continuous increase in BMD was shown with a dose of 10 mg per day, reaching 11.2% after 7 years of therapy. A second group of patients initially received 20 mg per day, followed by 5 mg per day, and finally placebo for the 6th and 7th year. In this group, BMD was maintained in the last 2 years, though the increase in bone turnover reflected by the bone markers suggests that BMD begins to decrease after this time. The persistence of a protective effect beyond treatment is characteristic of alendronate, in contrast to the situation observed with hormone replacement therapy.

Emkey et al. [41] have presented an update on 247 women from the same population after 10 years of follow-up. After 10 years of treatment with 10 mg per day, a cumulative 13.7% increase occurred in spinal BMD compared to baseline values. Between the 8th and 10th year, a 2.25% gain in vertebral BMD was seen, while in women administered 5 mg per day the gain in this same period was 1.6%. The values reached in hip and total body were maintained between years 8 and 10 of treatment. By contrast, BMD in the forearm remained stable in women treated with 10 mg daily, but decreased slightly in those given half that dose. The tolerability of such prolonged therapy was good for both doses compared with the group administered placebo between the 6th and 10th year of the study. The treated women administered 20 mg per day for 2 years, 5 mg per day for 3 years, and then 5 years of placebo showed BMD drops in non-vertebral measurements.

The results from Boivin et al. [29] support the hypothesis that the reduction in activation frequency caused by the antiresorptive effect of ALN is followed by a secondary mineralization that increases

the percentage of bone structure units having reached a maximum degree of secondary mineralization. These effects contribute to improved bone strength as demonstrated by the reduction in fracture incidence previously demonstrated in these patients. Masarachia et al. [42] reported that biopsies from osteoporotic women treated for 2 years with 5 mg per day oral ALN had higher trabecular bone volume, trabecular number and thickness, and trabecular connectivity than placebo-treated controls. It is reasonable to infer that the preservation of bone architecture may play a role in alendronate's anti-fracture efficacy.

Concern has been raised by some authors that bisphosphonates may initially increase the toughness of bone, and then with prolonged therapy, decrease it. Some animal studies indicate that microcrack density and length increase during treatment with high doses of bisphosphonates [43,44]. With extended suppression of remodeling, denser and more homogeneous regions of bone may form, which could allow a microcrack to travel with less energy through the structure. Nonetheless, the bones of the bisphosphonate-treated animals performed better in most mechanical tests than the controls. Furthermore, there is no evidence from clinical studies that prolonged treatment with bisphosphonates has a negative effect on fracture resistance. Indeed, the available data suggest that such treatment reduces fracture risk for up to 10 years [41,45]. However, further evidence is needed to determine the precise mechanisms of action in long-term treatment.

An essential question is the reliability of the treatments, i.e. the percentage of treated patients in whom a positive treatment effect is seen. In this sense, BMD significantly increased after 1 year of treatment with alendronate in over 90% of treated patients, and the percentage response was similar for both the 10 mg per day dose and for the 70 mg per week regimen [38].

In the *Fosamax International Trial* (FOSIT), which included over 1000 women with low BMD randomized to receive either alendronate or placebo for 1 year, the bisphosphonate was seen to have beneficial effects upon bone mass, biochemical parameters and symptomatic fractures [46]. The benefit on symptomatic fractures was apparent from the 3rd month of treatment, and a reduction in the risk of non-vertebral fractures of 47% in 1 year. In other words, the effects upon fractures are detected early after the start of therapy.

6. Effects of alendronate on risk fracture in women with postmenopausal osteoporosis: the FIT study

The *Fracture Intervention Trial* (FIT) is a large clinical trial designed to evaluate the effects of alendronate upon the frequency of vertebral and non-vertebral fractures in postmenopausal women with a low BMD and either with or without a history of previous fractures, i.e. the population included in the trial corresponds to the situation most frequently seen in daily clinical practice. Several publications have appeared as the results were obtained over the years [23,47–51]. The most significant data will be analyzed here.

The FIT was conducted with a data control system, independent of the study sponsor, which guarantees objective evaluation of fractures, product safety and other aspects. The inclusion criteria for the cases were very strict. As an example, 10% of the fractures were discarded due to a lack of evidence, and follow-up was also highly rigorous, so that 95% of the cases were controlled to the end of the study. The patients included were 6459 women postmenopausal for at least 2 years, with ages ranging from 55 to 81 years, and with a reduced hip BMD (under 0.69 g/cm²), as measured by dual energy absorptiometry. The study comprised two arms: 2027 women having any vertebral fracture documented by X-rays (FIT-1); and 4432 women without radiological evidence of prior vertebral fracture (FIT-2) (Table 1).

The women were randomized to treatment with alendronate (5 mg per day during 2 years and then 10 mg per day during 12–30 additional months) or placebo. The patients received an adequate intake of calcium with supplements and Vitamin D. As regards BMD,

after only 1 year of therapy with alendronate, BMD increased 3% or more in the total hip in 35% of the women, while 50% showed 1–3% increases, and 21% showed a decrease or no changes at this level. The women with the greatest increase in hip BMD in the first 12 months were those having a lesser incidence of new vertebral fractures: only 3.2% of the women with a BMD increase of 3% or more in total hip experienced vertebral fractures, as compared to 6.3% of fractures in women in whom BMD either failed to increase or decreased (RR = 0.45; CI = 0.27–0.72). The same type of relationship was found for BMD measured after 24 months, and after 3 years over 90% had shown significant BMD increases in the hip [47,48,51]. These results suggest that the incidence of new fractures is related to changes in BMD, and that the 1st and 2nd years of treatment correspond to the lowest incidence of vertebral fractures.

This study has shown that alendronate significantly reduces the number of hip fractures, statistical significance being reached after 18 months of therapy with a 63% reduction which was sustained throughout the study. The risk of hip fracture and the effect of alendronate upon fracture prevention depend upon the baseline BMD [48]. It is not clear why alendronate is more effective for preventing clinical fractures in the cases with lower BMD, but it should be noted that this appears to be a typical characteristic of all antiresorptive drugs (an identical effect has been seen for other bisphosphonates and raloxifene).

Lewis et al. [23] have recently shown that alendronate significantly reduces the risk of multiple symptomatic fractures after 6 months in a subgroup of women with osteoporosis who had at least one vertebral fracture at baseline or who had no prior

Table 1

Reduction of the incidence of skeletal fractures in postmenopausal women included in the FIT study and treated with alendronate (comparison with placebo in the control group); modified from Black et al. [47] and Cummings et al. [48]

	FIT-1		FIT-2		
	Percentage	P	Percentage	RR	95% CI
Hip fracture	–51	=0.047	–56	0.44	0.18–0.97
New vertebral fracture	–47	<0.001			
New multiple vertebral fracture	–90	<0.001			
Morphometric vertebral fracture			–44	0.56	0.39–0.80
Any clinical fracture ^a			–36	0.64	0.50–0.82

^a In women with an initial femoral neck T score of 2.5 or less.

fracture and a BMD value in the femoral neck of ≤ 2.5 standard deviations below normal or lower. Treatment consisted of 5 mg per day for 2 years, followed by 10 mg per day for the rest of the time, and the results were compared to those of a placebo group. All the women received calcium and Vitamin D supplements, and the mean follow-up was 4.3 years. Treatment with alendronate reduced the risk of multiple symptomatic fractures by 42% (RR = 0.58; CI = 0.41–0.81), and the risk of symptomatic vertebral fractures was reduced 84% (RR = 0.16; CI = 0.05–0.42). The cumulative incidence curve began to be divergent 3 months after starting treatment, and statistical significance was reached at 6 months ($P = 0.044$) for the symptomatic multiple vertebral fractures. When the whole follow-up period was considered, the rates of all symptomatic fractures and symptomatic vertebral fractures were, respectively, 34 and 63% lower than in the placebo group.

7. Alendronate in the prevention of bone mass loss without osteoporosis

Administration of alendronate prevents bone mass loss as measured by BMD in recently menopausal women without osteoporosis [52–54]. In the *Early Postmenopausal Intervention Cohort* (EPIC) study, the effects of two alendronate doses, 2.5 and 5 mg per day, were investigated during 4 years. The BMD increased approximately 4% in the vertebral spine and 3% in the hip with the 5 mg per day dose. The increases in BMD were similar to those achieved with HRT with estrogens and gestagen [52]. In the extension of this study, a group of women agreed to continue to 5 years and assess the effects of treatment discontinuation: 52 women received alendronate (5 mg per day) for 5 years (Group I), 56 received placebo for 3 years followed by alendronate (5 mg per day) for 2 years (Group II), and 52 received alendronate (20 mg) during 2 years and then no therapy for 3 years (Group III) [53]. At the end of the study, BMD increased in the spine and trochanter in the first group by 2.5 and 3.2%, respectively, and stabilized in femoral neck and total body comparison to baseline. The BMD results were similar after 5 years in the spine, hip and total body in Groups I and III. After the bisphosphonate was discontinued in the last 3 years in Group

III, BMD reduction was 1.8–5.7% from baseline values.

Luckey et al. [54] evaluated the efficacy and safety of alendronate 35 mg once weekly ($n = 362$) compared with alendronate 5 mg daily ($n = 361$) in the prevention of osteoporosis. The study was a 1-year, double-blind, multicenter study of postmenopausal women (6 months or greater), 40–70 years of age, with lumbar spine and femoral neck bone density T-scores between -2.5 and 1. Mean increases in lumbar spine BMD at 12 months were equivalent. BMD increases at other skeletal sites and effects on bone turnover were also virtually identical for the two dosing regimens. It seems that once-a-week administration, with no increase in side effects, would improve compliance in women with osteopenia or a strong family history of osteoporosis.

8. Tolerability of alendronate

The tolerability of long-term treatment with bisphosphonates has been analyzed in terms of histological safety and gastrointestinal tolerability [55]. Daily treatment with alendronate shows rates for adverse events, treatment discontinuation and loss of patients similar to other compounds. Safety in terms of the histological effects has been shown up to 3 years. Longer treatments, of up to 10 years, have shown good tolerability and few adverse effects [41], though it should be taken into account that this population was highly self-selected and motivated in comparison with the routine clinical population.

Although the tolerability of alendronate is good when the recommendations appropriate for bisphosphonates are followed, some patients consider its use inconvenient, particularly if they are taking multiple drugs. Weekly treatment with 70 mg has solved this problem, increasing treatment compliance rate with the same efficacy as the traditional daily dosing [56,57].

A multicenter study analyzed the gastrointestinal tolerability of a weekly dose of alendronate (70 mg) versus placebo administered for 12 weeks in persons with osteoporosis [58]. The primary study parameters were the incidence of any gastrointestinal adverse reaction, while secondary parameters included the number of patients discontinuing

medication and the changes in bone resorption assessed by the N-telopeptide/creatinine ratio. In a subgroup of cases, the influence of prior use of bisphosphonates was evaluated. Gastrointestinal adverse effects occurred in 11% of the cases treated with alendronate and in the 13% of subjects who received placebo. Treatment was discontinued by 3% of patients receiving the bisphosphonate, and by 1% of patients given placebo. The differences for the primary and secondary parameters were not statistically significant. On the other hand, the adverse effects were less common among the cases which had previously received bisphosphonate (8%) than in those which used the medication for the first time (16%). The urine N-telopeptide/creatinine values decreased after 12 weeks in the cases treated with alendronate. It can be concluded that the undesirable effects resulting from treatment are the same as those seen for placebo.

In an observational cohort of 11,916 patients under treatment with alendronate the events most frequently reported as suspected adverse reactions were gastrointestinal symptoms including dyspepsia, esophagitis, esophageal reflux, duodenitis, gastritis and heartburn. Serious suspected adverse reactions possibly related to alendronate were single reports of angioedema, erythema multiform, hypercalcemia and hypocalcemia [59].

9. Comparison of different antiresorptive drugs with alendronate

Antiresorptive treatments for postmenopausal osteoporosis have been studied from multiple perspectives. Marcus et al. [60] reviewed the many studies available. Estrogens and HRT can reduce the risk of vertebral and non-vertebral fractures. There is a meta-analysis of all interventional and observational studies made involving HRT with different primary objectives in which the incidence of fractures was recorded [61]. This meta-analysis shows that HRT has a favorable effect upon non-vertebral fractures, with a reduction in their incidence. This effect appears to be greater in the younger patient cohorts. The results recently published for the WHI study, a large observational, epidemiological study involving the follow-up of a cohort of healthy postmenopausal women,

show HRT to reduce the incidence of non-vertebral fractures [62].

The effects of SERMs, bisphosphonates and salmon calcitonin to increase BMD and reduce the risk of fractures have been shown in prospective and randomized studies, but the evidence is weak for calcitonin [28]. In these trials, the increases in lumbar BMD vary greatly from one product to another, while the reduction in fracture risk is similar, and there is no clear evidence of any reduction in non-vertebral fractures except for the bisphosphonates.

The Osteoporosis Research Advisory Group has analyzed in depth the information on the effects of antiresorptive drugs upon vertebral and non-vertebral fractures [30]. The results suggest that alendronate reduces the relative risk of vertebral fractures in a greater proportion than any other agent, and it is considered that the protection cannot be less than a third, while the combined results for raloxifene and risedronate should be no less than a quarter. As to reduction of the relative risk of non-vertebral fractures, the figure for alendronate is at least 31% (mean reduction 50%) versus at least 13% for risedronate (mean reduction 25%), while the rest of agents fall behind these bisphosphonates (Tables 2 and 3).

Direct comparison of the results obtained with different drugs is difficult, because the designs of the respective studies must be taken into account, as well as patient age at the time of entry to the study, the time from menopause, the use of calcium supplements and Vitamin D, the primary fracture parameter, the definition of vertebral deformity or fracture, the treatment discontinuation rate, and statistical power. A last point of caution is the value of BMD as surrogate parameter, since the relationship is uncertain and variable.

9.1. Direct comparison of alendronate versus risedronate

The so-called Study 159, a multinational, double blind, placebo-controlled trial, compared the efficacy during 1 year of weekly alendronate (70 mg) taken under fasting conditions 30 min before eating and drinking versus risedronate 5 mg daily 2 h after eating and 2 h before the intake of any food or drink, and a placebo group, in postmenopausal women [63]. All 549 women had been menopausal for at least 2 years, with an age range of 60–90 years, normal

Table 2
Magnitude of the effects of different agents upon the risk of vertebral fractures

Treatment	Number of studies (patients)	RR (95% CI)	P for RR
Calcium	5 (576)	0.77 (0.54–1.09)	0.14
Vitamin D	8 (1130)	0.63 (0.45–0.88)	<0.01
Alendronate (5–40 mg) 8 (9360)	0.52 (0.43–0.65)	<0.01	
Etidronate (400 mg)	9 (1076)	0.63 (0.44–0.92)	0.02
Risedronate	5 (2604)	0.64 (0.54–0.77)	0.01
Calcitonin	1 (1108)	0.79 (0.62–1.00)	0.05
Raloxifene	1 (6828)	0.60 (0.41–1.07)	0.01
HRT	5 (3117)	0.66 (0.41–1.07)	0.12
Fluorine	5 (646)	0.67 (0.38–1.19)	0.17

The number of studies is indicated, along with the total number of patients, the relative risk (RR) and 95% confidence interval (95% CI), and the statistical significance for RR (modified from Cranney et al. [30]).

baseline values of Vitamin D, no evidence of vertebral fractures in at least three of the first four lumbar vertebrae, and a BMD in the lumbar spine or hip of -2.5 standard deviations or more with respect to normal. All the patients received calcium and Vitamin D supplements. Alendronate showed a greater reduction in bone resorption and a greater increase in BMD than risedronate in the lumbar spine and in all hip sites. These results may be due to a greater antiresorptive efficacy of weekly alendronate, a lesser risedronate bioavailability, or both. In any case, authors such as Horchberg et al. [28], in a recently published meta-analysis evaluating the impact of changes in turnover and BMD upon fracture risk reduction with all the treatments available, found that therapies which increase bone mass to a greater extent and

produce greater reductions in turnover have a superior antifracture efficacy. The tolerability was similar for both products.

9.2. Direct comparison of alendronate versus calcitonin

Adami et al. [64] conducted a double blind comparative study with alendronate and calcitonin in postmenopausal women with osteoporosis who were divided into four groups: placebo, alendronate 10 mg per day, alendronate 20 mg per day, and intranasal calcitonin 100 U per day for 2 years. All the women received calcium supplements (500 mg per day). At the end of the 2nd year the change in BMD was 5.2% for the low dose of alendronate and 7.3% for the high

Table 3
Magnitude of the effects of different agents upon the risk of non-vertebral fractures

Treatment	Number of studies (patients)	RR (95% CI)	P for RR
Calcium	2 (222)	0.86 (0.43–1.72)	0.66
Vitamin D	6 (6187)	0.77 (0.57–1.04)	0.09
Etidronate	7 (867)	0.99 (0.69–1.42)	0.97
Alendronate (5 mg)	8 (8603)	0.87 (0.73–1.02)	0.09
Alendronate (0–40 mg)	6 (3723)	0.51 (0.38–0.69)	<0.01
Raloxifene	2 (6961)	0.91 (0.79–1.06)	0.24
Calcitonin	1 (1245)	0.80 (0.59–1.09)	0.16
Risedronate	7 (12958)	0.73 (0.61–0.87)	<0.01
HRT	6 (3986)	0.87 (0.71–1.08)	0.10
Fluorine	5 (950)	1.46 (0.92–2.32)	0.11

The number of studies is indicated, along with the number of total patients, the relative risk (RR) and 95% confidence interval (95% CI), and the statistical significance for RR (modified from Cranney et al. [30]).

dose in the lumbar spine; 3.8 and 4.6% in the femoral neck; and 7.1 and 7.5% in the trochanter, respectively. By contrast, calcitonin was unable to significantly increase BMD in the different skeletal points measured. Moreover, bone turnover markers were modified with the bisphosphonate, but not with placebo or calcitonin.

Downs et al. [65] directly compared treatment with oral alendronate (10 mg per day) versus intranasal calcitonin (200 U per day) and placebo for 12 months as treatment for osteoporosis in women with menopause for at least 5 years. The study excluded women with previous fractures or with a BMD of under 4 standard deviations. The three groups of women received calcium and Vitamin D supplements. The bisphosphonate induced greater BMD increases than calcitonin after 1 year of treatment: 5.16% versus 1.18% in the lumbar spine; 4.73% versus 0.47% in the trochanter; and 2.78% versus 0.58% in the femoral neck. Bone turnover parameters decreased more with alendronate than with calcitonin. However, the risk of fracture could not be evaluated in this study due to the limited duration.

10. Combined treatment with alendronate and hormone replacement therapy and alendronate and raloxifene

As regards the possibility of combined therapies, the administration of two antiresorptive agents causes a greater increase in BMD, but the effect of the combination upon risk fracture is not known. HRT is effective for the prevention of bone mass loss and fractures related to osteoporosis [61,62,66–69]. The combination of bisphosphonates and hormones is mutually reinforcing in the prevention and treatment of bone metabolic disorders [37,70–72]. Wimalawansa [70] showed that combined administration of etidronate and HRT for 4 years in menopausal women with osteoporosis caused a greater BMD increase in the lumbar spine and hip than any of the two products alone.

Lindsay et al. [71] studied 428 menopausal women with osteoporosis who were receiving HRT for 1 year and who were randomized to receive placebo or alendronate 10 mg per day in addition to HRT for another year. Combined treatment caused a significantly greater increase than HRT plus placebo in both vertebral (3.6% versus 1.0%; $P < 0.001$) and hip BMD

(2.7% versus 0.5%; $P < 0.001$). However, the differences were not significant for BMD in the femoral neck (1.7% versus 0.8%; $P = 0.072$). The tolerability of combined treatment was acceptably good.

Bone et al. [37] studied 425 postmenopausal women with low BMD values who had not previously received HRT. These women were randomized to alendronate 10 mg per day, 0.625 mg per day of conjugated equine estrogens, the combination of both products, or placebo for 2 years. All the women also received a daily supplement of 500 mg of calcium. At the end of the study, the therapeutic combination was seen to be more effective in increasing BMD than any of the other three treatment modalities. The increase achieved with the combined treatment involving HRT and alendronate was significantly greater than that provided by each of the monotherapies ($P < 0.001$). The reduction in bone-specific alkaline phosphatase was 60% for the combined treatment, 50% in the group given alendronate, and 49% in the women receiving HRT, with the differences being statistically significant for the combined treatment versus each of the individual therapies. The NTX values were 70, 61, and 52%, respectively, and were again significantly different for the combined treatment as compared to each of the individual treatments. There were no statistically significant differences between alendronate and HRT in monotherapy. During the study no significant adverse effects were recorded in any of the groups. Based on these observations, it may be speculated that combined treatment would be appropriate in women with very low BMD, and in women who lose bone mass despite estrogen treatment but who wish to continue taking these hormones for other reasons, such as the prevention of vasomotor or genital symptoms.

Palomba et al. [72] have evaluated the effectiveness of estrogens plus low-dose alendronate on bone metabolism in a prospective randomized, double-blind, placebo-controlled, clinical trial with a total of 150 surgically postmenopausal women with osteoporosis. The three treatment groups were Group A, micronized E2 (2 mg per day) plus standard-dose alendronate (10 mg per day); Group B, micronized E2 plus low-dose alendronate (5 mg per day); and Group C, micronized E2 plus placebo (one tablet per day). After 2 years, BMD significantly increased compared with baseline in all groups. The percentage BMD change was significantly higher in Groups A and B

than in Group C. The differences in BMD detected between Groups A and B were not statistically significant. It seems that in surgically postmenopausal osteoporotic women treated with estrogen replacement, the addition of alendronate at a low dose of 5 mg daily induces a gain of bone mass not significantly different in comparison with that obtained using a standard dose of 10 mg daily.

The combination of alendronate and HRT has additive effects, with BMD increases superior to those achieved by each treatment alone.

Both alendronate and raloxifene reduce bone turnover markers, increase BMD, and prevent vertebral fractures, though alendronate, but not raloxifene, has been consistently shown to prevent non-vertebral fractures. Johnell et al. [73] conducted a randomized double-blind study of 331 menopausal women with osteoporosis to assess the value of combined treatment with raloxifene (60 mg per day) and alendronate (10 mg per day) for 1 year. Vertebral BMD increased 2.1% with raloxifene, 4.3% with alendronate, and 5.3% with the combined treatment. The increase in BMD of the femoral neck was greater with the combined treatment (3.7%) than with either raloxifene (1.7%) or alendronate alone (2.7%). Although the observed bone marker changes were almost twice as important in magnitude for alendronate versus raloxifene, it is not certain whether these differences are important for fracture risk, though they are likely so [28]. It is not clear whether the increased gain in BMD with the combined treatment reflects a lesser risk of fracture compared to monotherapy. Despite these results, there is no evidence to indicate the convenience of routine use of the combined treatment, since the latter has not been shown to have a greater antifracture effect, the adverse effects may be additive, and the costs are doubled. Nevertheless, and as discussed for the combination of alendronate and HRT, these results may suggest that combined treatment could be appropriate in women with very low BMD values, or in women who lose bone mass despite raloxifene treatment but who wish to continue using the latter drug for other reasons. This point is more questionable and controversial than in the case of HRT, since the benefits of raloxifene in other organic systems, such as in the prevention of breast cancer, are pending confirmation in prospective clinical trials designed for this purpose.

A potentially interesting indication for alendronate in relation to HRT is in those patients with risk factors for osteoporosis or in osteoporotic individuals in whom HRT is discontinued due to intolerability, poor compliance, or based on the results of the WHI study (it should be remembered that this study showed the risk/benefit ratio for HRT beyond 5 years of continuous treatment to be questionable, requiring individualization in each case). The results of a prospective, randomized and placebo-controlled study involving 144 patients who abandoned HRT have been recently reported [74]. They were randomized to receive either a daily dose of 10 mg of alendronate sodium or matching placebo. Spine, hip, and total body BMD; biochemical markers of bone turnover; and tolerability were the main outcomes. This study showed that HRT discontinuation was followed by a bone mass loss similar to that which would have been seen in these same women due to the menopausal process in the absence of treatment. In fact, the group receiving placebo following HRT lost an average of 3.2% (95% CI, -4.6 to -1.7%) in spine BMD as compared to a 2.3% mean increase (95% confidence interval [CI], 1.7–3.0%) in patients treated with alendronate for 1 year. Greater hip and total body BMD preservation was also observed with alendronate use. Bone turnover decreased significantly with alendronate, but increased in the placebo group. Alendronate was well tolerated, with no increase in adverse events compared with placebo. Therefore, alendronate appears to prevent the bone mass loss which follows HRT discontinuation. This may be important for those patients in whom HRT was prescribed for osteoporosis or osteopenia, among other reasons, and for all menopausal women with risk factors for osteoporosis who have received HRT, since in both instances following treatment discontinuation the protective effect is lost in only a short time, and the fracture risk may be expected to increase.

11. Final remarks

The primary objective of treating osteoporosis is to substantially reduce risk of fractures. ALN is an important drug for the treatment of osteoporosis because they inhibit bone resorption, increase bone density and, therefore, decrease risk of fractures. Given that treatment for osteoporosis should be long term,

compliance and tolerability are important. The side effect profile of ALN is similar to that of placebo. In clinical practice, oesophagitis has rarely been reported and in most cases seems to be related to inappropriate administration.

Although bisphosphonates reverse the low rate of remodeling and resorption and increase tissue mineral content and thereby bone mass, we do not know why the fracture risk is reduced but not abolished, the precise value of bone density as a surrogate measure for antifracture efficacy, and the most adequate duration of ALN treatment. More research is needed to identify new fracture reduction strategies that will allow better matching of risk factors and treatments. We also need well designed comparative studies, head to head, with other agents currently used for the treatment of osteoporosis and prevention of fractures.

In women with documented osteopenia, or a strong family history of osteoporosis, a low dose of ALN has been shown to increase and maintain bone density and reduce fractures.

It is necessary to develop clinical methods to study bone quality during antiresorptive treatments to assess bone structure and function. Finally, the only property of bone that we would need to know would be its ability to resist fracture.

References

- [1] Moynihan R, Heath I, Henry D, Gøtzsche PC. Selling sickness: the pharmaceutical industry and disease mongering. Medicalisation of risk factors. *BMJ* 2002;324:886–91.
- [2] Moynihan R. Marketing: celebrity selling. *BMJ* 2002; 324:1342.
- [3] Rapid responses to Moynihan et al. 2002. <http://www.bmj.com/cgi/eletters/324/7342/886>.
- [4] Anderson ME. Putting the record straight. <http://www.bmj.com/cgi/eletters/324/7349/1342#23332>.
- [5] Peacock M, Turner CH, Econs MJ, Foroud T. Genetics of osteoporosis. *Endocr Rev* 2002;23:303–26.
- [6] Riggs BL, Khosla S, Melton III LJ. Sex steroids and the construction and conservation of the adult skeleton. *Endocr Rev* 2002;23:279–302.
- [7] Cauley JA. Risk of mortality following clinical fractures. *Osteoporos Int* 2000;11:556–61.
- [8] National Osteoporosis Foundation. 1996 and 2015 Osteoporosis prevalence figures. State-by-State Report. Washington, DC: National Osteoporosis Foundation; 1997. Executive summary, 1, 2.
- [9] American Cancer Society. Cancer facts & figures-1996. Atlanta (GA): American Cancer Society; 1996. p. 11.
- [10] American Heart Association. 1997 Heart and stroke statistical update, vol. 11. Dallas (TX): American Heart Association; 1996. p. 14.
- [11] Lindsay R, Silverman SL, Cooper C, Hanley DA, Barton I, Broy SB, et al. Risk of new vertebral fracture in the year following a fracture. *JAMA* 2001;285:320–3.
- [12] Ott S. Osteoporosis and bone physiology. World Health Organizations definitions. [<http://www.uwcmec.org/courses/bonephys/whodef.html>].
- [13] National Osteoporosis Foundation. Physician's guide to prevention and treatment of osteoporosis. Belle Mead (NJ): Excerpta Medica; 1999.
- [14] Weinstein L, Ullery B. Identification of at-risk women for osteoporosis screening. *Am J Obstet Gynecol* 2000;183:547–9.
- [15] Kovacs KA. Decision rules for bone mineral density testing. *CMAJ* 2002;167:509.
- [16] Lydick E, Cook K, Turpin J, Melton M, Stine R, Byrnes C. Development and validation of a simple questionnaire to facilitate identification of women likely to have low bone density. *Am J Manage Care* 1998;4:37–48.
- [17] Cadarette SM, Jaglal SB, Murray TM, McIsaac WJ, Joseph L, Brown JP. Evaluation of decision rules for referring women for bone densitometry by dual-energy X-ray absorptiometry. *JAMA* 2001;286:57–63.
- [18] Michaëlsson K, Bergström R, Mallmin H, Holmberg L, Wolk A, Ljunghall S. Screening for osteopenia and osteoporosis: selection by body composition. *Osteoporos Int* 1996;6:120–6.
- [19] Nelson HD, Helfand M, Woolf SH, Allan JD. Screening for postmenopausal osteoporosis: a review of the evidence for the US Preventive Services Task Force. *Ann Intern Med* 2002;137:529–41.
- [20] Wasnich RD, Miller PD. Antifracture efficacy of antiresorptive agents are related to changes in bone density. *J Clin Endocrinol Metab* 2000;85:231–6.
- [21] Masud T, Francis RM. The increasing use of peripheral bone densitometry. *BMJ* 2000;321:396–8.
- [22] Bell NH, Bilezikian JP, Bone HG, Kaur A, Maragoto A, Santora AC. MK-063 Study Group. Alendronate increases bone mass and reduces bone markers in postmenopausal African-American women. *J Clin Endocrinol Metab* 2002;87:2792–7.
- [23] Levis S, Quandt SA, Thompson D, Scott J, Schneider DL, Ross PD, et al. FIT Research Group. Alendronate reduces the risk of multiple symptomatic fractures: results from the Fracture Intervention Trial. *J Am Geriatr Soc* 2002;50:409–15.
- [24] Meunier PJ, Boivin G. Bone mineral density reflects bone mass but also the degree of mineralization of bone: therapeutic implications. *Bone* 2000;21:373–7.
- [25] Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. *BMJ* 1996;312:1254–9.
- [26] Schott AM, Cormier C, Hans D, Favier F, Hausherr E, Dargent-Molina P, et al. How hip and whole body bone

- mineral density predict hip fracture in elderly woman: the EPIDOS prospective study. *Osteoporosis Int* 1998;8:247–54.
- [27] Faulkner KG. Bone matters: are density increases necessary to reduce fracture risk? *J Bone Miner Res* 2000;15:183–7.
- [28] Hochberg MC, Greenspan S, Wasnich RD, Miller P, Thompson DE, Ross PD. Changes in bone density and turnover explain the reduction in incidence of nonvertebral fractures that occur during treatment with antiresorptive agents. *J Clin Endocrinol Metab* 2002;87:1586–92.
- [29] Boivin GY, Chavassieux PM, Santora AC, Yates J, Meunier PJ. Alendronate increases bone strength by increasing the mean degree of mineralization of bone tissue in osteoporotic women. *Bone* 2000;27:687–94.
- [30] Cranney A, Wells G, Willan A, Griffith L, Zytaruk N, Robinson V, et al. II. Meta-analysis of alendronate for the treatment of postmenopausal women. *Endocr Rev* 2002;23:508–16.
- [31] Pérez-López FR. Alendronato y tratamiento hormonal sustitutivo en la osteoporosis femenina. In: Pérez-López FR, editor. *Climaterio y envejecimiento. Medicina basada en la evidencia*. Zaragoza: SEISGE; 1999. p. 273–92.
- [32] Watts WB. Bisphosphonates therapy for postmenopausal osteoporosis. *South Med* 1992;85(Suppl):2–31.
- [33] Brown DL. Developments in the therapeutic applications of bisphosphonates. *J Clin Pharmacol* 1999;39:651–60.
- [34] McClung MR. Bisphosphonates in osteoporosis: recent clinical experience. *Exp Opin Pharmacother* 2001;1:225–38.
- [35] Jeal W, Barradell LB, McTavish D. Alendronate: a review of its pharmacological properties and therapeutic efficacy in postmenopausal osteoporosis. *Drugs* 1997;53:415–34.
- [36] Plotkin LI, Manolagas SC. Prevention of osteocyte and osteoblast apoptosis by bisphosphonates and calcitonin. *J Clin Invest* 1999;104:1363–74.
- [37] Bone HG, Greenspan SL, McKeever C, Bell N, Davidson M, Downs RW, et al. Alendronate and estrogen effects in postmenopausal women with low dose bone mineral density. *J Clin Endocrinol Metab* 2000;85:720–6.
- [38] Schnitzer T, Bone HG, Crepaldi G, Adami S, McClung M, Kiel D, et al. Therapeutic equivalence of alendronate 70 mg once-weekly and alendronate 10 mg daily in the treatment of osteoporosis. *Aging Clin Exp Res* 2000;12:1–12.
- [39] Tonino RP, Meunier PJ, Emkey R, Rodríguez-Portales JA, Menkes CJ, Wasnich RD. Skeletal benefits of alendronate: 7-year treatment of postmenopausal osteoporotic women. *J Clin Endocrinol Metab* 2000;85:3109–15.
- [40] Rizzoli R, Greenspan SL, Bone III G, Schnitzer TJ, Watts NB, Adami S, et al. Two year results of once-weekly administration of alendronate 70 mg for the treatment of postmenopausal osteoporosis. *J Bone Miner Res* 2002;17:1988–96.
- [41] Bone HG, Hosking D, Devogelaer JP, Tucci JR, Emkey RD, Tonino RP, et al. Ten-year experience with alendronate for osteoporosis in postmenopausal women. *New Engl J Med* 2004;350:1189–99.
- [42] Masarachia P, Howard T, Santora A. Alendronate increases trabecular bone connectivity in elderly osteoporotic women. *J Bone Miner Res* 2003;18(Suppl 2):S372.
- [43] Mashiba T, Hirano T, Turner CH, Forwood MR, Johnston CC, Burr DB. Suppressed bone turnover by bisphosphonates increases microdamage accumulation and reduces some biomechanical properties in dog rib. *J Bone Miner Res* 2000;15:613–20.
- [44] Mashiba T, Turner CH, Hirano T, Forwood MR, Jacob DS, Johnston CC, et al. Effects of high-dose etidronate treatment on microdamage accumulation and biomechanical properties in beagle bone before occurrence of spontaneous fractures. *Bone* 2001;29:271–8.
- [45] Sorensen OH, Crawford GM, Mulder H, Hosking DJ, Gennari C, Mellstrom D, et al. Long-term efficacy of risedronate: a 5-year placebo-controlled clinical experience. *Bone* 2003;32:120–6.
- [46] Pols HAP, Felsenberg D, Hanley DA, Stepan J, Muñoz-Torres M, Witkin TJ, et al. Multinational, placebo-controlled, randomized trial of the effects of alendronate on bone density and fracture risk in postmenopausal women with low bone mass: results of the FOSIT study. *Osteoporosis Int* 1999;9:461–8.
- [47] Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. *Lancet* 1996;348:1535–41.
- [48] Cummings SR, Black DM, Thompson DE, Applegate WB, Barrett-Connor E, Musliner TA, 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;280:2077–82.
- [49] Watts NB. Treatment of osteoporosis with bisphosphonates. *Endocrinol Metab Clin N Amer* 1998;27:419–39.
- [50] Black DM, Thompson DE, Bauer DC, Ensrud K, Musliner T, Hochberg MC, et al. Fracture risk reduction with alendronate in women with osteoporosis: the Fracture Intervention Trial. *J Clin Endocrinol Metab* 2000;85:4118–24.
- [51] Hochberg MC, Ross PD, Black D, Cummings SR, Genant HK, Nevitt MC, et al. Larger increases in bone mineral density during alendronate therapy are associated with a lower risk of new vertebral fractures in women with postmenopausal osteoporosis: Fracture Intervention Trial Research Group. *Arthritis Rheum* 1999;42:1246–54.
- [52] Ravn P, Bidstrup M, Wasnich RD, Davis JW, McClung MR, Balske A, et al. Alendronate and estrogen-progestin in the long-term prevention of bone loss: four-year results from the Early Postmenopausal Intervention Cohort Study: a randomized trial. *Ann Intern Med* 1999;131:935–42.
- [53] Ravn P, Weiss SR, Rodríguez-Portales JA, McClung MR, Wasnich RD, Gilchrist NL, et al. Alendronate in early postmenopausal women: effects on bone mass during long-term treatment and after withdrawal. Alendronate Osteoporosis Prevention Study Group. *J Clin Endocrinol Metab* 2000;85:1492–7.
- [54] Luckey MM, Gilchrist N, Bone HG, Davie MW, de Villiers TJ, Wu M, et al. Therapeutic equivalence of alendronate 35 milligrams once weekly and 5 milligrams daily in the prevention of postmenopausal osteoporosis. *Obstet Gynecol* 2003;101:711–21.

- [55] Kherani RB, Papaioannou A, Adachi JD. Long-term tolerability of the bisphosphonates in postmenopausal osteoporosis: a comparative review. *Drug Saf* 2002;25:781–90.
- [56] Stone M. Once-weekly treatment for osteoporosis. *Hosp Med* 2002;63:230–2.
- [57] Izarra Pérez L, Medrano Sanidefonso M, Paleo ME, the members of the Satisfaction, Preference and Compliance with Biphosphonates Study Group. Satisfaction, preference and compliance with alendronate and risedronate in postmenopausal women with osteoporosis. In: *Proceedings of the Third International Meeting on Social and Economic Aspects of Osteoporosis and Osteoarthritis*, Barcelona, 7–9 noviembre 2002. abstract 0110/2.
- [58] Greenspan S, Field-Munves E, Tonino R, Smith M, Petruschke R, Wang L, et al. Tolerability of once-weekly alendronate in patients with osteoporosis: a randomized, double-blind, placebo-controlled study. *Mayo Clin Proc* 2002;77:1044–52.
- [59] Biswas PN, Wilton LV, Shakir SA. Pharmacovigilance study of alendronate in England. *Osteoporos Int* 2003;14:507–14.
- [60] Marcus R, Wong M, Heath 3rd H, Stock JL. Antiresorptive treatment of postmenopausal osteoporosis: comparison of study designs and outcomes in large clinical trials with fracture as an endpoint. *Endocr Rev* 2002;23:16–37.
- [61] Torgerson DJ, Bell-Syer SEM. Hormone replacement therapy and prevention of non-vertebral fractures: a metaanalysis of randomised trials. *JAMA* 2001;285:2891–7.
- [62] Writing group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. *JAMA* 2002;288:321–33.
- [63] Hosking D, Adami S, Felsenberg D, Andia JC, Valimaki M, Benhamou L, et al. Comparison of change in bone resorption and bone mineral density with once-weekly alendronate and daily risedronate: a randomised, placebo-controlled study. *Curr Med Res Opin* 2003;19:383–94.
- [64] Adami S, Passeri M, Ortolani S, Brogginini M, Carratelli L, Caruso I, et al. Effects of oral alendronate and intranasal salmon calcitonin on bone mass and biochemical markers of bone turnover in postmenopausal women with osteoporosis. *Bone* 1995;17:383–90.
- [65] Downs Jr RW, Bell NH, Ettinger MP, Walsh BW, Favus MJ, Mako B, et al. Comparison of alendronate and intranasal calcitonin for treatment of osteoporosis in postmenopausal women. *J Clin Endocrinol Metab* 2000;85:1783–8.
- [66] Gallagher JC, Baylink DJ, Freeman R, McClung M. Prevention of bone loss with tibolone in postmenopausal women (2002) results of two randomized, double-blind, placebo-controlled, dose-finding studies. *J Clin Endocrinol Metab* 2001;86:4717–26.
- [67] Greendale GA, Espeland M, Slone S, Marcus R, Barrett-Connor E. Bone mass response to discontinuation of long-term hormone replacement therapy: results from the Postmenopausal Estrogen/Progestin Interventions (PEPI) Safety Follow-up Study. *Arch Intern Med* 2002;162:665–72.
- [68] Wu F, Ames R, Clearwater J, Evans MC, Gamble G, Reid IR. Prospective 10-year study of the determinants of bone density and bone loss in normal postmenopausal women, including the effect of hormone replacement therapy. *Clin Endocrinol* 2002;56:703–11.
- [69] Pérez-López FR. Tratamiento hormonal de la menopausia: controversias, precisiones y perspectivas. *Med Clin (Barc)* 2003;120:148–55.
- [70] Wimalawansa SJ. A four-year randomized controlled trial of hormone replacement and bisphosphonate, alone or in combination, in women with postmenopausal osteoporosis. *Am J Med* 1998;104:219–26.
- [71] Lindsay R, Cosman F, Lobo RA, Walsh BW, Harris ST, Reagan JE, et al. Addition of alendronate to ongoing hormone replacement therapy in the treatment of osteoporosis: a randomized, controlled clinical trial. *J Clin Endocrinol Metab* 1999;84:3076–81.
- [72] Palomba S, Orio Jr F, Colao A, di Carlo C, Sena T, Lombardi G. Effect of estrogen replacement plus low-dose alendronate treatment on bone density in surgically postmenopausal women with osteoporosis. *J Clin Endocrinol Metab* 2002;87:1502–8.
- [73] Johnell O, Scheele WH, Lu Y, Reginster JY, Need AG, Seeman E. Additive effects of raloxifene and alendronate on bone density and biochemical markers of bone remodeling in postmenopausal women with osteoporosis. *J Clin Endocrinol Metab* 2002;87:985–92, comment in: *J Clin Endocrinol Metab* 2002;87:983–984.
- [74] Ascott-Evans BH, Guañabens N, Kivinen S, Stuckey BG, Magaril CH, Vandormael K, et al. Alendronate prevents loss of bone density associated with discontinuation of hormone replacement therapy: a randomized controlled trial. *Arch Intern Med* 2003;163:789–94.