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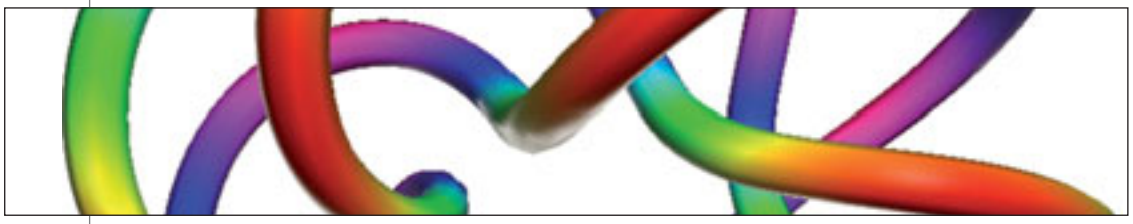

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Epidemiology of osteoporotic fractures. Mortality and morbidity

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Introduction

The osteoporotic fracture has an enormous economic impact, in addition to its effects on health. In the year 2000, it was estimated that there were 4 million new fractures in Europe – some 8 fractures per minute, or one fracture every 8 seconds[1]. Of these, 0.89 million were hip fractures. The direct costs have been estimated at nearly 32 billion euros, which it is expected will increase to 77 billion euros by 2050 as a function of demographic changes expected in Europe[2].

The combined risk of suffering hip, forearm and clinical vertebral fractures is approximately 40%, similar to that of developing cardiovascular disease[3]. In Caucasian women, the risk of hip fracture over their lifetime is 1/6, higher than that of suffering breast cancer -1/9-[4].

In our country it is calculated that 2 million women have osteoporosis, putting its prevalence at 26.1% of women over 50 years of age[5]. More than 25,000 fractures appear annually, from which originate direct costs of more than 126 million euros, with indirect costs reaching 420 million euros annually[6].

Incidence and prevalence

The incidence of fractures is bimodal, with peaks in young people and in older people. In young people the predominant fractures are of the large bones, normally after intense trauma, and with greater frequency in males. Although in this group bone resistance is not usually in question, the available data show that this factor may play some role in its pathogeny[7]. From 35 years of age, the incidence of fractures in women ascends gradually until it is double that of males. Before the availability of studies which assessed radiographic vertebral fractures in place of clinical fractures, it was thought that this peak was due to fractures of the hip and forearm. These studies have proved that vertebral fractures contribute significantly to this incidence (Figure1).

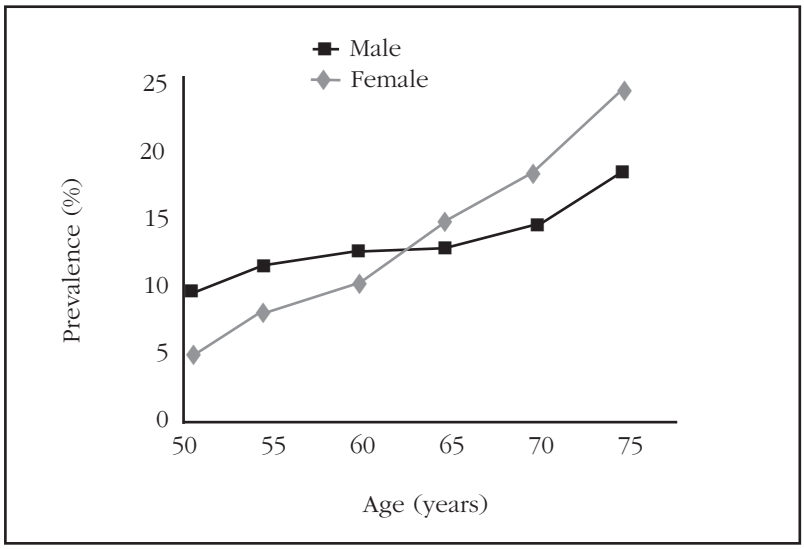
Fracture of the hip

In most populations the incidence of hip fracture increases exponentially with age (Figure 1). From the age of 50, the women to man ratio approximates to 2 to 1[8]. In conjunction with this, 98% of hip fractures appear in people over the age of 35 years and 80% in women (given that women predominate in later years). Most occur after a fall from a height equal to or less than their own.

Recent studies of the database of the General Practitioners of the United Kingdom (General Practice Research Database, GPRD), which includes 6% of the population, has characterised the incidence of fractures adjusted for age and sex[8]. The global risk of hip fracture from 50 year of age in the United Kingdom is 11.4% and 3.1% for women and men, respectively. The greater part of this risk accumulates in the more advances ages in such a way that the risk of suffering a hip fracture in the following 10 years at 50 is 0.3% while at 80 years the risk is 8.7% - in the case of males 0.2% and 2.9% respectively.

Hip fractures have a seasonal influence, with a higher incidence in the winter, even though they occur principally in people's homes, which seems to suggest that this is due to worse conditions of illumination or a slowing of neuromuscular refle-

Figure 1. Incidence of fractures of the hip, radiographic vertebral and forearm, according to age and sex (adapted from refs 17 and 15)



xes in colder periods. The direction and way of falling is significant, with a lateral fall directly on the hip more likely to cause a fracture than a frontal forward fall[9].

The incidence varies substantially from one population to another and is usually higher in Caucasians than in other races. Across Europe, the proportion of hip fractures varies up to 7 times between different countries, with our country being among those with a low incidence[10], and Norway, Sweden, Iceland, Denmark and the USA considered to have a high incidence[11]. Thus, environmental factors have an important role in the aetiology of hip fractures, although those studied to date – smoking, alcohol consumption, physical activity, ethnic origin and/or migratory status – have not completely explained these differences.

In our country, a retrospective study which assessed 13,195 hip fractures found a clear dominance of the female sex (74%) with an average age of 80.7 ± 8.4 years. The average incidence was 6.94 ± 0.44 fractures of the hip for each 1,000 inhabitants per year. The prospective study from this same work found a monthly prevalence of 0.60 ± 0.04 fractures per 1,000 inhabitants with 74% being women and an average age of 81.4 ± 8.1 years. The authors conclude that the average prevalence in 2003 was 7.20 fractures per 1,000 inhabitants, of whom a third had suffered a previous hip fracture and only 18% having previously received medical treatment for osteoporosis[12].

Vertebral fracture

The data from the European Vertebral Osteoporosis Study (EVOS) have shown over recent years that the standardised prevalence by age for vertebral fracture in Europe is 12.2% for men and 12.0% for women between 50 and 79 years of age[13]. The prevalence of fractures by age and sex in this population are shown in Figure 2. Although classically, it had been thought that vertebral fractures were more common in men than in women, the data from the EVOS study show that this is not so at younger ages; the prevalence of deformities at between 60 and 75 years is similar, or even higher in men, possibly due to a higher incidence of traumas. The majority of vertebral fractures in older women happen in daily activities such as picking up or lifting objects more than because of falls. Many vertebral fractures are asymptomatic and, what is more, there is no unanimous agreement regarding the radiographic definition of vertebral deformities. In studies which use radiographic screening, the incidence of vertebral deformities has been estimated as being three times those of the hip, although only a third of those result in a medical consultation[14]. The data from the EVOS study have allowed a more precise assessment of radiographic vertebral fractures in a broad population. Between the years of 75 and 89, the incidence of vertebral fractures is 13.6 per 1,000 inhabitant years in men and 29.3 per 1,000 person years for women[13], which is clearly higher than the 0.2 per 1,000 person years in men and 9.8 per 1,000 person years assessed in people between 75 to 85 years defined through clinical presentation in an earlier study in the US[15]. The standardised global incidence from the EVOS study was 10.7 per 1,000 person years in women and 5.7 per 1,000 person years in men.

From the comparison of the population data available, it is evident that the heterogeneity of the prevalence of vertebral fractures is much lower than that found in fractures of the hip. This contrasts with the much lower variability between populations of vertebral fractures identified by clinics or through hospitalisation.

Distal forearm fracture

The Colles fracture has a presentation profile different from that of the hip and the vertebrae. There is an increase in the incidence in Caucasian women between 45 and 60 years of age followed by a plateau[16], which has been related to a change in neuromuscular reflexes caused by aging, and by a tendency to suffer lateral or backward falls whose impact they are attempted to avoid or cushion with the arms extended. The majority of these wrist fractures appear in women and more than 50% appear in women over 65 years of age. The GPRD database shows a risk of vital fracture in women of 50 years of age of 16.6%, whilst at 70 years this risk falls to 10.4%. The incidence in males is significantly lower and does not change excessively with age (rest of life risk of 2.9% at 50 years and 1.4% at 70[17].

Table 1. Risk factors for osteoporotic fracture

	High risk	Moderate risk
Mixed (Associated with BMD + independent component)	Advanced Age Personal History of Osteoporotic Fractures Maternal History of Hip Fractures Low weight* Glucocorticoids** High remodelled bone	Diabetes Mellitus Smoking
Associated with low BMD	Hypogonadism in males Primary HyperPTH Primary HyperPTH Anorexia Nervosa Prolonged immobilisation Anticomicials Malabsoprtion	Feminine sex Early menopause*** Amenorrhea Rheumatoid Arthritis Hyperthyroidism Vitamin D deficit Low intake of calcium****

High risk: relative risk > 2. Moderate risk: relative risk > 1 y < 2. *Body mass index: < 20 kg/m^2. **Period superior to 3 months and but of 7,5 mg prednisone/day. ***Before 45 years. ****Inferior to 500-850 mg/day. The factors related to the falls tendency and associated with the production of fractures are condidered independent factors. BMD: bone mineral density.

Temporal projections

The progressive aging of the population, especially in the western world, but also in developing countries, will produce a spectacular increase in the number of osteoporotic fractures. In fact, between 1990 and 2000, a worldwide increase in hip fractures of 25% was reported. The peak for the presentation of hip fractures appears at 75-79 years of age in both sexes; for the other fractures the peak appears at 50-59 years and reduces with age[1]. For 2050, the projection of the incidence of vertebral fractures is predicted to increase by 310% in males and 240% in women[18].

However, recent European studies have shown that the incidence, adjusted for age and sex, of hip fractures has been reducing over the last decade[19,20]. The steady growth in weight in the West and better screening and treatment for osteoporosis have been suggested as reasons for this reduction, which could counteract the progressive aging of the population of Europe.

Tendency to the aggregation of fractures in individuals

In different epidemiological studies it has been suggest that patients with fragility fractures have an increased risk of developing other types of fractures. Thus, for example, a previous vertebral deformity increases from 7 to 10 times the risk of developing later vertebral deformities[21]. The risk of suffering a second hip fracture is also increased by a similar magnitude. North American data show an increased risk of hip fracture of 1.4 times in women and of 2.7 times in men after suffering a Colles fracture[22]. The increased risk of a later vertebral fracture in the same cohort is 5.2 and 10.7 times. The EVOS study[23], has shown that existing vertebral deformities predict an increased risk of hip fractures occurring of between 2.8 and 4.5 times, which increase with the number of deformities and their intensity. The incidence of new vertebral fractures in the year after the appearance of a vertebral fracture is 19.2%, and the accumulated incidence over 10 years of any type of fracture after an earlier fracture is 70%[24]. All these data, taken together, show the importance of taking appropriate therapeutic measures after the diagnosis of an osteoporotic fracture.

Risk factors for fractures

There are many factors associated with the risk of developing osteoporotic fractures. Some of these, notable among which is bone mineral density as the most predictive, directly influence bone resistance, while others are related to falls and their characteristics. All these factors interact in each individual in a complex way. Although a detailed review of these factors is outside the scope of this chapter, Table 1 lists the principal factors according to SEIOMM's clinical practice guide[25].

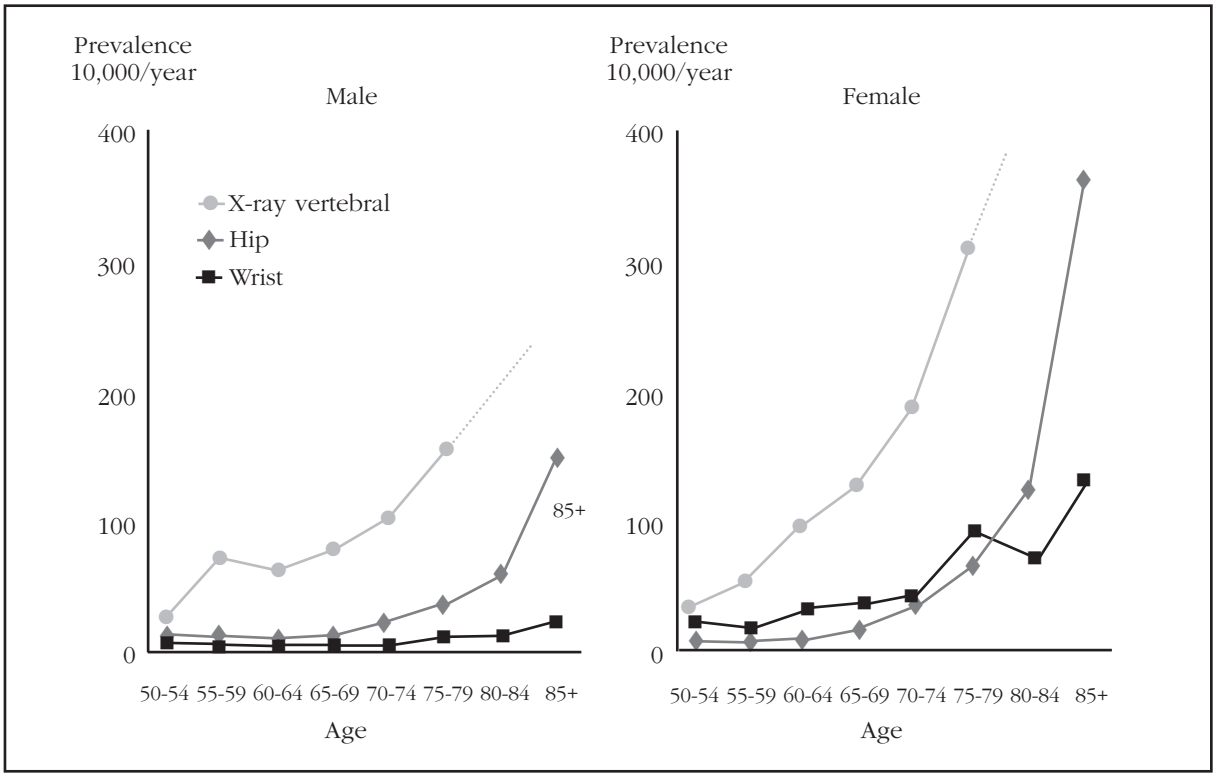
Mortality after osteoporotic fracture

The patterns of mortality after the most frequent types of fractures have been studied. In the Rochester, USA cohort the rate of survival 5 years after suffering a hip or vertebral fracture was 80% of that expected in men and women without fracture of a similar age[14]. In our country, 13% of patients who have suffered a fracture die in the following 3 months. In the two years after the fracture, mortality reaches 38%[6].

Mortality of hip fracture

The mortality associated with fractures of the hip is higher in men than in women and increases with age, as well as in those subjects with major co-morbidities and a worse functional state pre-

Figure 2. Prevalence of vertebral deformities by sex (adapted from ref. 13)



fracture[14]. Around 8% of men and 3% of women of more than 50 years of age die while hospitalised due to fractures. In the United Kingdom, survival after suffering a fracture of the hip is 63.6% in men as against an expected 90.0%, and in women 74.9% as against the 91.1% expected[17]. The risk of death is maximum immediately after the fracture and reduces gradually with time. The cause of death is not usually attributed to the fracture directly, but to other co-morbidities present.

Mortality after vertebral fracture

In contrast to what occurs with hip fractures, vertebral fractures are associated with an increased risk of death later in the year after the fracture[14]. Again, the excess risk appears to be due to co-morbidities present, but differently from the case with hip fractures, it worsens over time. In the GPRD study the survival observed a year after suffering a vertebral fracture was 86.5% against 93.6% expected. At five years, the survival observed was 56.5% against the 69.9% expected[17].

Morbidity after osteoporotic fracture

In the USA, 7% of the survivors of any type of fracture have some kind of permanent limitation and 8% require chronic hospital care. On average, a white north American woman of 50 years has a 13% probability of suffering a functional deterioration after any kind of fracture[26]. In our country 45% of patients who have suffered a vertebral fracture are left with functional damage and up to 50% can develop total or partial disability[6].

Morbidity after hip fracture

As in relation to mortality, hip fractures are the main cause of later morbidity. Patients with hip fracture have a propensity to develop of acute complications such as ulcers due to decubitus, broncho-pneumonia and infections of the urinary tract. Perhaps the most significant complication in the long term is difficulty in deambulation which appears in 50% of cases. Age is a key determinant of what happens after the fracture: while only 14% of subjects receiving a fracture between 50 and 55 years of age are sent to hospital for chronic care, up to 55% of those over 90 years of age need to continue to receive chronic care[26].

Morbidity after vertebral fracture

In spite of the scarce or zero symptomology of the majority of vertebral fractures, their high frequency makes them responsible for a great number of hospitalisations: almost 2,200 a year in England and Wales in patients older than 45 years of age. The principal consequences of a vertebral fracture are back pain, kyphosis and loss of height. The scores of the specific quality of life test (QUALEFFO) diminish in line with an increase in the number of vertebral fractures[27].

Morbidity after distal forearm fractures

Fractures of the distal forearm do not appear to increase morbility[17]. While fractures of the wrist can impact adversely on daily activities such as writing or cooking, few patients are left completely incapacitated. However, up to 50% of those

subjects who suffer such a fracture state that they have a poor functional state 6 months on from the fracture[26].

Conclusions

Osteoporosis is a disease which has an enormous impact on public health, both from the point of view of the individual, and collectively for health systems, economies and populations. The epidemiological characterisation and better knowledge of the risk factors for osteoporotic fractures, combined with the development of drugs of proven efficacy, puts us in an excellent position for the development of preventative and therapeutic measures, both populational, as well as for those individuals at high risk.

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Adherence in the treatment of osteoporosis

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Summary
Therapeutic compliance is of great importance if the demonstrable efficacy of drugs is to be reproduced in clinical practice. It has been sufficiently demonstrated that there is a lack of adherence in the pharmacological treatment of osteoporosis. The factors which influence this are highly diverse and complex, with some dependent on the treatment itself, whether in the drug (efficacy, secondary effects) or in its administration regime (frequency, mode of administration). The appearance of every day more efficacious drugs, with more spaced out administration periods and modes of administration which reduce undesirable secondary effects, diminish considerably the rate of abandonment of treatment for osteoporosis. However, these improved drugs should be complemented with an appropriate doctor-patient relationship, aimed at instructing and educating the latter and at maintaining their interest, to achieve a proper adherence to treatment, and thus, the maximum efficacy of the drugs.

Introduction. The size of the problem
The importance of osteoporosis lies in the fact that it predisposes the appearance of fractures, which means that it constitutes a major health problem[1,2]. The fractures most commonly associated with osteoporosis are vertebral, hip and the distal radius, or Colles, fractures[3]. It has been estimated that the risk of a patient with osteoporosis of suffering any fracture during the rest of their life varies between 40-50% in women and between 13% and 22% in men, and, in the specific case of hip fracture, the risk for a white woman is 17.5%, while for a man it is 6% [1,2,4].

All these fractures have a high level of morbidity and result in a high social-health cost[4,5]: for example, approximately 25% of vertebral fractures and practically all fractures of the hip require hospitalisation[2]. But, in addition, osteoporotic fractures, especially of the hip, have a considerable mortality. Indeed, studies carried out in this country show that at the end of one year after a hip fracture approximately 30% of patients have died, increasing to 40% when the follow up is extended to two years[6-10]. Other studies have described a reduction in survival at 5 years of 15% after a hip fracture, observing that the greater part of the deaths occur in the first six months after it[2].

Osteoporosis is a chronic process, usually asymptomatic, which deteriorates the bone, making it susceptible to fracture. The ultimate objective in the treatment of osteoporosis is to minimise the risk of suffering new fractures[11-14]. There is no drug which reduces this risk to zero: most of the drugs available nowadays for the treatment of osteoporosis obtain reductions of between 40% and 65%[11-14], even when the medication is taken continuously during a period of time which varies between 3 and 5 years. These circumstances (lack of symptoms, necessity for prolonged treatment) means that, as happens with other similar diseases (arterial hypertension, hypercholesterolemia, diabetes mellitus), the abandonment by the patient of their medication is common, and for many diverse reasons. Institutions such as the World Health Organisation and the American Heart Association recognise that one of the main problems in the treatment of chronic diseases in developed countries is non-compliance on the part of patients in the correct taking of their medicines[15,16].

With reference specifically to osteoporosis, multiple studies have demonstrated deficiencies in adherence to treatment by patients, and this has

been studied with all drugs used: calcitonin, oestrogen therapy, raloxifen, teriparatide and biphosphonates[17-22], and some have even compared the abandonment of osteoporosis treatment depending on which drug is being used. The existing works are highly varied, and often have contradictory results[23-28]. The disparity in the populations studied and the methodologies applied explain the difficulties in comparing results. However, all these studies agree on the fact that adherence to osteoporosis treatment is, in general, low, and that in the first year the percentage abandonment is found to be between 30% and 50% in most cases.

The success of treatment for osteoporosis depends to a great extent on adherence

It is evident that those patients who take their medicine for osteoporosis regularly have better results, both in reference to changes in bone mineral density[29], and, more importantly, in the reduction of the rate of fractures and a decrease in mortality[30,31]. A study carried out by Siris et al. in a broad population of postmenopausal women of over 45 years of age, for whom had been indicated a biphosphonate as a treatment for osteoporosis, showed that, after 2 years of follow up, those women who took the treatment correctly (43%) had a reduction of risk of fracture, both vertebral and non-vertebral, 21% higher than those patients who did not correctly follow the treatment[32]. Earlier, Caro et al. had obtained similar results, finding a reduction in the appearance of new fractures higher (16%) among those patients who were compliant, as opposed to those who were not. In this study the period of follow up was also 2 years, and the drugs evaluated were calcitonin, hormone replacement therapy and biphosphonates[33]. The same authors repeated the study, using a broader database, with a cohort of more than 38,000 women affected by osteoporosis, and obtained similar figures: poor adherence to treatment was associated with an increase in the risk of fracture of 17% after a follow up of 1.7 years[34]. These results are corroborated by those obtained in other studies[35,37].

The appropriate adherence to treatment is not only beneficial for the health of the patients, but also results in improved cost-effectiveness for the drug therapy for osteoporosis[38].

The importance of the frequency of administration in the adherence to treatment for osteoporosis

Poor adherence to treatment for osteoporosis is dependent on many factors[39,40]. We have already indicated at the start that low or zero symptomology of the disease, and its being chronic, are two of the most important. Other factors which have an influence on adherence are patient-dependent: age, state of health, socio-cultural position. Others are dependent on the medical action taken (motivation, follow up, carrying out of tests which identify the state of the disease). And finally, there are factors dependent on the type of drug used in the treatment: secondary effects, efficacy, mode and frequency of administration. Therefore, adherence is complex and difficult to quantify[41]. The modification of the factors which negatively influence treatment compliance is one of the objectives all professionals should have when antiosteoporotic therapy is prescribed.

Up until now, the main interest in improving adherence has been centred on drug-dependent factors. In general, the drug treatments for osteoporosis have few secondary effects, and only a few infrequent effects could be considered to be serious. On the other hand, over time ever more efficacious and powerful drugs have been developed, varying the modes of administration and lengthening the frequency of dosage, all intended, ultimately, to improve adherence[42,43].

The biphosphonates and adherence in the treatment of osteoporosis

The biphosphonates constitute the group of drugs most used in the treatment of osteoporosis[44,45], and are considered to be the first choice for the treatment of osteoporosis in our ambit[46]. The gastrointestinal secondary effects of the biphosphonates, the motive for abandonment of treatment in a high percentage of cases[47], necessitated the finding of preparations whose administration was more spaced out, and whose mode of administration was different from oral: what were initially daily doses became weekly administration in the case of alendronate[48] and risedronate[49], and monthly oral administration became quarterly intravenous in the case of ibandronate[50,51]. The last biphosphonate to be marketed for the treatment of osteoporosis, zoledronate, is for annual, intravenous administration[52], which ensures, at least, compliance and therapeutic efficacy over a year, which is very important in view of the high number of abandonments of treatment which happen over this period[53-55].

So, all these changes in the administration regimes of the biphosphonates can improve adherence in the long term drug treatment of osteoporotic patients[56,57]. The beneficial results of this have been demonstrated in different studies. Penning van Best et al. used a database in the Netherlands of the dispensation of drugs over a year, and found that, of 2,124 women who started therapy with biphosphonates, 51.9% of those to whom the drugs were administered weekly continued treatment, but only 42% of those taking a daily dose continued treatment, with different types of biphosphonates used (etidronate, alendronate or risedronate)[58]. Cramer et al. studied 2,741 women in treatment with biphosphonates and observed that, at the end of a year, persistence was 44.2% in those who had taken the biphosphonates weekly, as against 31.7% among those who took them daily[59].

In another study carried out in the United States, Ettinger et al. analysed the sale of prescriptions of alendronate and risedronate in more than

211,000 women. They found that, at the end of a year, 56.7% of those patients who had taken biphosphonates weekly continued to receive the drug, as against 39% of those who had taken it daily. However, the authors noted that more than 40% of patients did not continue with treatment with weekly biphosphonates, and suggested that formulations which allowed a more spaced out administration could improve therapeutic compliance[60]. Cramer et al. in a work carried out in a total of 15,640 women in the United Kingdom, France and the United States, found that after a year, the persistence of patients with biphosphonates was higher in those who received the medication weekly, compared to those who received it daily: 44% vs 32% respectively in the Untied States; 52% vs 40% in the United Kingdom; and 51% vs 44% in France; in all cases the value of $p < 0.001$[61].

In the study known as PERSIST, adherence to treatment at 6 months in a group of women who received ibandronate monthly was compared with another group which took alendronate weekly, and it was found that 56.6% of those who took the monthly treatment continued with treatment as opposed to 38.6% of those who took alendronate weekly[62]. We have not found a study which compares the adherence to treatment between biphosphonates with an annual dose and those administered more frequently.

On the other hand, there are studies whose objective was to record the preferences of patients with osteoporosis in respect to the pharmacological preparations for their treatment, in which it was observed that, as a general rule, patients prefer a more spaced out administration of treatment[63-65]. A multicentric, randomised, double blind study carried out by McLung et al. to assess the safety and efficacy of a single intravenous dose of 5 mg of zoledronic acid vs 70 mg of alendronate taken orally, weekly, carried out in 225 women with postmenopausal osteoporosis who had previously received weekly treatment with alendronate, found that 78.7% of patients expressed their preference for an annual intravenous treatment as opposed to a weekly oral treatment[66], equal to that stated by the majority of patients participating in a similar study carried out by Saag et al.[67].

However, although a higher adherence to treatment is seen with doses at longer intervals, it is notable that almost all the studies also conclude that the percentage of patients receiving the correct medication is sub-optimal, and this is the case whatever the mode of administration. This indicates that, as we have suggested earlier, therapeutic compliance in osteoporosis is complex, and dependent on diverse factors not only related to the drug, but also to the patient and their surroundings, as well as to the medical action taken. A review by Cochrane, Hayes et al.[68] indicates that patients take approximately half the medication prescribed. Analysing a series of interventions taken to increase adherence to treatment, they found that those that were sure to be efficacious in the long term were complex to implement. Included amongst these interventions were provision of detailed information, self-monitoring by patients, advice, telephone reminders, family support and psychological treatment. But they concluded that, taken as a whole, the results were rather poor, recommending that new studies dealing with the improvement of adherence to treatment be carried out.

In view of these results, it is evident that the inclusion in the therapeutic arsenal for osteoporosis of more powerful drugs, which can be administered at greater intervals of time and in ways which cause fewer secondary effects, increase considerably adherence to treatment. But we should not forget that in conjunction with these improved drugs we should address other adherence factors related to the patients themselves, as well as proceeding with medical/health interventions which support and promote therapeutic compliance.

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Osteoporosis: Concept and importance. Clinical picture

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Introduction

Osteoporosis is a common disease, responsible in great part for the fractures which occur in people over 50 years of age. Due to diverse pathogenic mechanisms a reduction in bone mass is produced, which is accompanied by an increase in bone fragility. Osteoporotic fractures are a health problem of great magnitude due to their repercussions not only in the health and quality of life of the patient, but also for the economic and social costs which its treatments and their side effects brings.

Definition of osteoporosis

Osteoporosis has probably accompanied humanity since its existence, but the current concept and definition are very recent. The definition was decided in two key meetings of experts, the first in 1993[1] and the more recent one, organised by the NIH in March 2000[2], from which resulted two separate consensus documents. In the first of these, osteoporosis was defined as "a systematic skeletal disorder characterised by the reduction in bone mass and alterations in the microarchitecture of bone tissue, with the consequent increase in the fragility of bone and its susceptibility to fracture"[1]. In the consensus of the year 2000, the definition was simplified to indicate that it consisted of a disease "in which bone resistance is deteriorated, which predisposes it to fracture". In addition, it was specified that " bone resistance is the result of the integration of the density and quality of bone"[2]. Viewed in this way, it is considered that a compromise of biomechanical function (resistance) happens not only due to the loss of quantity, but also due to the deterioration of other elements, such as the microarchitecture, on which the quality of bone depends. No mention was made of aetiopathogenic causes or mechanisms, given that they could influence more than one causal factor, and there are various pathogenic mechanisms from which could result in a reduction in bone resistance. It is very interesting that from the clinical point of view only the fracture is mentioned, which could reflect the poor clinical expression of the disease during its development before the fracture.

Much time has passed in achieving a consensus on this concept since the first observation in 1830, when Jean Lobstein confirmed some larger than usual holes in some human bones, which he described as porous, giving birth to the term osteoporosis. Its recognition as a clinical entity is due to Fullen Allbright, who described postmenopausal osteoporosis in 1940 and related it to a reduction in oestrogen[3]. The concept remained for a long time as the equivalent of loss of bone mass. The continuation of this error has, without a doubt, been contributed to by the definition of densitometric osteoporosis proposed by the working group of the World Health Organisation (WHO) which met in 1992[4].

It is important to distinguish between the two definitions which coexists at the moment. They represent two different approaches to the same problem, the diagnosis and assessment of risk of fracture on the one hand, and the conceptual definition on the other. Densitometric classification is an operational proposal for the assessment of risk of fracture using bone mineral density (BMD) cut-off points to diagnostic ends. It is worth remembering that a densitometric diagnosis of osteoporosis does not mean an absolute indication for treatment. And, on the contrary, some patients with

low bone mass, but not low enough to be diagnosed with osteoporosis, may have fractures. It is already indicated in the WHO technical report cited, that other parameters such as age, speed of bone loss or frequency of falls should be taken in to account[4]. This approach towards the assessment of risk of fracture is preferable. The existence of osteoporosis, or diminished bone mineral density, is one more piece of data to be included in the assessment of the patient. Recently, the WHO study group has proposed a tool for the calculation of risk of fracture called FRAX, which includes a series of clinical parameters in addition to BMD for the evaluation of the risk of fractures[5]. From the practical and therapeutic points of view the approach which centres on the patient according their risk of fracture is more useful, than the more simplistic approach which sees osteoporosis only in densitometric terms.

Some bone parameters

In the definition some concepts are introduced such as the mass, microarchitecture, resistance, density and quality of bone.

Bone mass and bone mineral density are related to the quantity of bone. Bone mass increases during the first decades of life until it reaches its maximum called "peak bone mass", at between 20 and 30 years of age[6]. It is possible to measure bone mass *"in vivo"* by calculating the BMD, which is expressed in g/cm^2. Low bone mass is the consequence of two variables: the peak bone mass achieved in youth and bone loss at later stages. Osteoporosis is usually the consequence of bone loss in adults, however, an individual who does not reach their optimum bone mass during youth may develop osteoporosis without there being great bone loss. So, insufficient bone growth in childhood and adolescence is as important as later bone loss in the development of osteoporosis[2]. The WHO has established an operational definition based on levels or cut-off points of BMD for white postmenopausal women. Thus, normal values of BMD are considered to be those above -1 (SD) in relation the average for young adults (T-score > -1); osteopenia entails values of BMD between -1 and -2.5 SD (T-score between -1 and -2.5); osteoporosis entails BMD values lower than -2.5 DE (T-score lower than -2.5) and established osteoporosis is when along with the above conditions are associated one or more osteoporotic fractures[4]. However, this classification should be used for epidemiological studies, but it should not be used in individuals as the sole criterion for the assessment of the patient. BMD only explains 70% of bone fragility[7]. For this reason, in the consensus of the year 2000, another element of bone resistance was introduced, which is bone quality.

Microarchitecture is one of the components not directly related to bone mass which was already introduced into the definition of osteoporosis in 1993. Loss of bone affects bone mass and its microarchitecture, and is especially important for the resistance of trabecular bone. The increase in the fragility of bone, when the number and thickness of trabeculae are reduced, has been confirmed in numerous biomechanical studies[8]. Techniques currently possible allow knowledge of bone microarchitecture and its resistance *"in vivo"* by means of methods such as the micro-TC, and, although at the moment only used by researchers, may become useful for the clinical evaluation of patients in the not too distant future[9].

Bone quality is one component of resistance, along with bone density[10]. It is a broad term, but integrated into bone quality are considered to be some parameters such as microarchitecture, turnover, damage accumulation and bone mineralisation. In a more generic way one may think of quality all those elements related to bone resistance, as distinct from bone mass.

Risk of fracture

A fracture occurs when a force, such as a trauma, is applied to an osteoporotic bone. In this sense, osteoporosis is a risk factor for fragility fractures. From the data of numerous epidemiological studies diverse risk factors for low bone mass and fractures have been identified. It is useful to distinguish between two types of risk factor, since some are related to the BMD, and therefore with suffering osteoporosis, while the rest are associated with osteoporotic fracture, whose prevention should be the principle objective of therapeutic interventions. Some of the risk factors for low bone mass can be seen in Table 1. Greater consideration should be given to risk factors for fracture, such as low BMD itself, and others, independent of BMD, among which are found previous history of fragility fractures, family history of osteoporotic fractures, thinness, active smoking, consumption of alcohol and an increase in bone turnover[11]. Not all these factors have the same predictive force for fractures and notable for their clinical importance are personal or family history of fractures[12-15].

Some extraskeletal circumstances may influence the mechanism of production of fractures. Hence, it is useful to remember that fractures depend on the concurrence in an individual of a fragile bone and a fall. It is not surprising that the frequency of falls is also associated with a higher risk of fractures[16].

When the development of a cohort is observed it is possible to check how a group with negligible fragility fractures occurs in subjects with BMD above the level of osteoporosis[17]. Therefore, strategies directed at the detection of those individuals with osteoporosis are insufficient to prevent fractures. It would seem to be more profitable to direct that effort to the identification of individuals with a high risk of fractures. Hence, the estimation of absolute risk at 10 years allows the approximation of reality with greater objectivity. The WHO has proposed a software tool FRAX, available online, which allows the evaluation of the absolute risk of fracture at 10 years[5]. The calculation is made using an algorithm which includes BMD and

a series of independent clinical factors which are included in Table 2. The strongest clinical factors, in addition to the BMD, are age, personal history of fracture, family history, consumption of corticoids and the existence of rheumatoid arthritis.

Aetiopathology

In the last decade we have seen a revolution in the understanding of bone biology. Part of the intricate network of cytokines, growth factors and the cell's participation in the regulation of bone metabolism and how to modify these cellular signals in different situations are now understood. Osteoporosis is the consequence of an alteration in bone remodelling which consists of an imbalance which favours resorption over formation. The result is low bone mass, and changes in the microarchitecture[18]. There are various types of osteoporosis which can be classified into two groups, primary and secondary[19].

The most common type of osteoporosis is postmenopausal, which is linked to two conditions, the menopause and aging. In women the ceasing of ovary function, and the consequent reduction in oestrogens, is accompanied by a phase of accelerated bone loss. Treatment by substituting the oestrogens reverses, to a great degree, this situation. The oestrogens reduce osteoclastogenesis by means of a complex, and not yet completely understood, interaction of cellular signals and bone cells[20]. Their deficiency increases resorption and the loss of bone mass and structure, which translates into bone fragility.

Another type of primary osteoporosis is involutive osteoporosis, which affects both men and women, and which is more associated with aging. The existence of a negative calcium balance and a certain degree of secondary hyperparathyroidism have been the pathogenic mechanisms linked to this bone loss. However, recent studies suggest that oestrogen deficiency may play a significant role in later stages of life, regulating the homeostasis of extraskeletal calcium. The oestrogens may modulate the cacium balance, favouring its intestinal absorption and limiting its renal elimination. In addition, an active influence of the oestrogens in the metabolism of vitamin D and its capacity to reduce the secretory reserve of parathormone (PTH), has been described. These circumstances have allowed the development of a unitary model of involutive osteoporosis, in which the deficiency of oestrogens plays a central role[21].

Male osteoporosis is less frequent than postmenopausal osteoporosis. From the point of view of using the BMD, recommended as cut-off points for an indication of postmenopausal osteoporosis are a T-score below -2.5 of the average for the young population[22]. The occurrence of primary osteoporosis in males appears to be lower than that for women. In the first situation the production mechanism is principally of an involutive type.

The causes of secondary osteoporosis are those which are produced as a consequence of a disease, or from taking pharmaceutical drugs. The most common is osteoporosis due to glucocorticoids. The risk of fracture is independent of BMD and is both related to the daily dose and the accumulated dose. Yet, even doses lower than 7.5 mg/day of prednisone, or equivalent, increase the risk of vertebral fracture when the accumulated dose is lower than 1g[23]. When the treatment with glucocorticoids is withdrawn the risk of fracture goes down, but remains higher in relation to patients who have not taken them[24]. In general, we may consider that half those patients treated for 6 months with glucocorticoids will have osteoporosis. The greatest bone loss is produced during the first 3 months of treatment due to its effect in inhibiting the apoptosis of the osteoclasts[25]. This action is by empowered by an increase in the apoptosis of the osteoblasts with a reduction in bone formation. The adverse effects of treatment also reach the muscle, which is atrophied, in turn, losing force and resistance, which presents a risk of falls.

Table 1. Some risk factors for low bone mass

Not modifiable	Modifiable
Age	Little physical exercise (sendentarism)
Sex (female)	Diet poor in calcium
Genetic	Hyperproteic diet
Menopause	Smoking
Hypogonadism	Alcohol abuse
Endocrinal diseases: Cushing, primary hyperparathyroidism, hyperthyroidism	Thinness (BMI < 19 kg/m^2)
Rheumatological diseases: Rheumatoid arthritis	Glucocorticoids
Nutritional diseases: malnutrition anorexia nervosa	Immunosuppressors
Disease of the digestive system: celiac disease, severe hepatopathies	Anticoagulants
Neoplasias: multiple myeloma	Heparin
	Proton pump inhibitors

Importance of osteoporosis

Osteoporosis has a great impact on the general population. Osteoporotic fractures impose a load of great magnitude from a socioeconomic point of

Table 2. Variables included in the FRAX tool

- Age
- Sex
- Weight
- Stature
- Previous fracture
- Parents with hip fracture
- Active smoker
- Taking glucocorticoids
- Rheumatoid arthritis
- Secondary osteoporosis
- Excessive consumption of alcohol
- BMD in femoral neck, which nuances the overall result of the other variables

view. It is a very common disease which affects 150-200 million people in the world. Approximately half of these patients come from the developed countries of North America, Europe and Japan. In general terms, it is estimated that around 33% of women over the age of 50 years will suffer from osteoporosis. Although measures have been proposed to reduce the problem, osteoporosis continues to be under-diagnosed and many patients, even with fractures recognisable as osteoporotic, remain without treatment. The social and political measures are not yet sufficient to address the prevention of this serious socio-health problem.

In addition to the personal repercussions due its high morbi/mortality, osteoporosis generates considerable socioeconomic costs. The analysis of these costs carry a high degree of uncertainty. The calculation is difficult and unreliable, since the available information is incomplete[26].

The costs, as is logical, are not limited to the pharmacological or surgical interventions. They are divided into direct and indirect costs. Among the first are those due to hospitalisation, outpatient care and drugs. These may be related to immediate assistive, social and hospital care, both short and long term, and to drugs. The costs of hospitalisation can be seen to be influenced by its duration. Within the outpatient care are included visits to the traumatologist, visits to other doctors, including the general practitioner, nurse visits, physiotherapy, occupational therapy and telephone assistance. Counted in the direct non-medical costs are social care and informal care. Services to be taken into account within social care, among others, are adaptations to the home, home health care, general home help and transport. Finally, among indirect costs, should be considered as key the loss of production of the patient, or of the family who looks after them[27]. On the other hand, the reduction in quality of life related to health has a significant social and individual cost.

Clinical manifestations

Osteoporosis is an asymptomatic disease. For this reason it has been called the "silent epidemic"[4]. It is a mistake to consider that bone loss is accompanied by musculoskeletal pain, and it is relatively common that patients are referred for this reason with the suspicion of osteoporosis, especially women in the peri- or first years of the menopause.

The principle clinical manifestations are due to its complications, fractures. The most frequent fragility fractures are located in the spinal column, the wrist and the hip. They are usually classified in a more general way as vertebral or non-vertebral. Among the non-vertebral fractures are also included those of the humerus, pelvis, ribs and other less frequent types. Not usually included as osteoporotic fractures are those of the finger, and cranium, but there are some doubts about fracture of the ankle[21].

They are produced by a minor trauma, such as a simple fall from a standing position. For this reason also, they are known as fragility fractures. They appear principally after the age of 50 years, and that differentiates them from the traumatic fractures which predominate in youth. The clinical manifestations of these fractures are the same as other fractures in the same location, and are accompanied with pain, loss of functional power and deformity[29].

The vertebral fracture is the most prevalent. Its typical clinical presentation form is acute pain, although not infrequently it can be asymptomatic. It can be the consequence of a mechanical effort in carrying or lifting weight, but also can have no apparent cause. The most typical manifestation is acute, intense pain located in the spine, which is exacerbated with movement and reduces with rest. This becomes very incapacitating, impeding sleep. The intensity of the pain usually reduces after the first 2-3 weeks, before disappearing after 2-3 months. The pain may radiate towards the ribs or the legs, according to whether it proceeds from the dorsal or lumbar spine. However, almost two thirds of vertebral fractures are asymptomatic and can only be confirmed by means of radiography of the lumbar or dorsal spine. For this reason these are classified as clinical or morphometric fractures, the latter only evident through imaging techniques[30,31]. In some patients, as a consequence of structural changes in the spine there may develop an instability of the spine, with paraspinal muscular contraction, ligamentous tension and incongruity in the articular facets which may be the cause of chronic axial pain[32].

Thoracic vertebral fractures usually have a "cradle" compression from which originates the characteristic kyphosis of these patients ("the

widow's hump"). In lumbar fractures the vertebrae are usually squashed in height the centre (devil's vertebrae). The loss of height of the vertebral bodies reduces the distance between the ribcage and the pelvis, which in some patients even results in the establishment of painful contact between the ribs and pelvis (costo-pelvic syndrome). The accumulation of vertebral crushing is translated into a loss of height. Some authors consider that a reduction of more than 3 cm in two years may be a sign of vertebral fractures. It has been proposed that the span of the higher extremities, a measure equal to the body height in youth, be compared with the height of the patient to detect reductions in height. It is of considerable interest that rarely in osteoporotic vertebral fractures are observed the neurological complications which accompany vertebral fractures of a different origin[33]. The appearance of medullary or radicular neurological manifestations should make us think of a non-osteoporotic origin for a fracture[32]. These modifications in the spine may cause difficulties in thoracic movement and affect breathing. The abdomen loses capacity , and becomes prominent, with consequent modification the intestinal tract. The most serious fracture is that of the hip, generally triggered by a fall. Although there are no data which support it, it has become common belief that in the presence of significant osteoporosis, the patient fractures their hip standing up, after which they fall. The highest rate of mortality associated with osteoporosis is related to hip fracture and represents one of its most significant social costs. The causes of death are diverse and in many cases are not directly related to the fracture[34]. The mortality is 20-30% in the first year, which means that the risk of death increases by 2 to 10 times that expected in a population with similar characteristics[35]. Most cases require surgical intervention. But the repercussions of a hip fracture are not limited to its hospital treatment, but also to the deterioration of the quality of life. The majority of patients have residual disability and a percentage of cases lose the capacity to live an independent life. For example, only a fifth of those patients who walked unaided before the fracture can do so 6 months after it[27].

The Colles fracture has fewer repercussions than the two earlier ones. Some patients can experience persistent local pain, functional incapacity, neuropathy and posttraumatic arthritis; in addition, it is a significant risk factor for future presentation of vertebral or hip fractures[27]. Finally, the psychological and social impact should be taken into account, which may result in osteoporotic fractures. The development of depression is the psychological disorder most frequently cited. The appearance of anxiety, fear of new fractures, and other emotional reactions are also important, and influence the recuperation of those patients[36]. The repercussions on families of patients with hip fracture and often with a great physical and psychological dependency, cannot sensibly be calculated due to their complexity.

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Zoledronic acid in the treatment of osteoporosis

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Introduction

Nowadays we have available a highly varied therapeutic arsenal for the treatment of osteoporosis[1]. The biphosphonates constitute the group of drugs most commonly used for the treatment of this disease and are the first choice according to the SEIOMM guides[2]. Among the biphosphonates, zoledronic acid is the most potent third generation nitrogenated biphosphonate currently on the market[3,4]. Its action mechanism means that it has a great affinity with the hydroxyapatite crystals of bone, above all in those areas of high bone turnover, reducing the speed of bone remodelling. In turn it is released during bone resorption and internalised by the osteoclasts, which interfere in the metabolism and function of these cells, and favour their apoptosis[5]. Zoledronic acid has an affinity for bonding with hydroxyapatite higher than other biphosphonates[6] and is the most powerful inhibitor of farnesyldiphosphate-synthase and of bone resorption[7].

Zoledronic acid is the first drug which allows annual treatment in postmenopausal patients affected by osteoporosis, or at high risk of fracture. The administration of 5 mg of zoledronic acid once a year has been shown to be efficacious in the reduction in risk of vertebral fractures in patients with postmenopausal osteoporosis or hip fracture due to a recent light trauma[8]. In turn it produces an increase in bone mineral density and a reduction in markers for bone turnover[9]. Being generally well tolerated, its annual administration makes it a comfortable and efficacious treatment option, in such a way that the patient's adherence to treatment is not a problem, thus maintaining the protection of bone over a whole year.

Therapeutic efficacy

a) In patients with postmenopausal osteoporosis

The reference study for the therapeutic efficacy of zoledronic acid in the treatment of postmenopausal osteoporosis is called Health Outcomes and Reduced Incidence with Zoledronic Acid Once-Yearly (HORIZON-PFT)[8]. It consists of a multicentre, randomised, double blind, placebo-controlled trial of three years duration, which compared the efficacy of a single intravenous perfusion of 5 mg of zoledronic acid lasting 15 minutes, against a placebo.

In order to carry out this study a total of 7,765 patients were selected, between 65 and 89 years of age, with a T-Score ≤ -2.5 in the femoral neck, with or without data indicative of existing vertebral fracture, or patients with a T-Score of ≤ -2.5 and radiological proof of at least two light vertebral fractures or one moderate vertebral fracture. Those patients previously treated with antiresorptive drugs were permitted to participate, with the patients being classified into two groups as a function of whether or not they had previously taken drugs against osteoporosis. The patients to whom a cleansing period could be applied, were randomly allocated to one of the groups. The first group included patients who had not taken any permitted drugs (calcitonin, raloxifen, tibolone, hormonal therapy, tamoxifen, ipriflavone, medroxyprogesterone), whilst in the second group were classed patients who had taken permitted antiosteoporotic drugs. This excluded patients who had taken, at any time, parathryroid hormone, sodium and strontium fluoride, anabo-

lics or somatropin in the 6 months, or systemic corticosteroids, orally or intravenously, in the 12 months, prior to their incorporation into the trial. Blood concentrations of calcium higher than 2.75 mmol/l or lower than 2.00 mmol/l, or a creatinine clearance of lower than 30.0 ml/minute in either of the two baseline visits, were also exclusion criteria. 3,889 patients were randomly assigned to receive a single perfusion of 5 mg zoledronic acid over 15 minutes, and 3,876 to receive a placebo at the baseline, at 12 months and at 24 months. All the patients received between 1,000 and 1,500 mg of calcium and between 400 and 1,200 UI of vitamin D orally.

The principal evaluation criteria were: the appearance of a new vertebral fracture (in those patients not treated with concomitant medication against osteoporosis) and/or the hip fracture (in all patients). The secondary evaluation criteria were bone mineral density, markers for bone turnover and results in terms of safety.

I. Effect on incidence of fracture

The objective of any antiosteoporotic treatment is the prevention of fractures, wherever they are located. After three years of study, the incidence of morphometric vertebral fractures in the group treated with a placebo was 10.9% as against 3.3% in the group treated with 5 mg of zoledronic acid administered intravenously over 15 minutes. This means a significant reduction ($p<0.001$) in the risk of morphometric fractures of 70% (relative risk: 0.30; CI 95%: 0.24 to 0.38). Significant reductions were also observed in the relative risk (RR) of these fractures in the group benefiting from zoledronic acid after one year (1.5% against 3.7% in the placebo group), and after two years (2.2% against 7.7%: RR 0.29), of treatment (Table 1).

The treatment with zoledronic acid resulted in a reduction of 41% in the risk of hip fracture. During these three years, the incidence of hip fracture was 2.5% in the group treated with a placebo and 1.4% in that treated with zoledronic acid (razón de riesgo instantáneo) hazard ratio: 0.59; CI 95%: 0.42 to 0.83). In comparison with the incidence in the placebo group, the incidence of non-vertebral, clinical and clinical vertebral fractures was reduced significantly in the group treated with zoledronic acid. These reductions were 25%, 33% and 77% respectively ($p<0.001$ for all the comparisons) (Table 1).

II. Effect on bone mineral density and biochemical markers

The HORIZON-PFT study also associated zoledronic acid with a significant improvement in bone mineral density and markers for bone metabolism[9]. The changes in BMD in the hip after three years of study were +4.1% in the group treated with zoledronic acid, as against -1.9% in the group treated with the placebo; +6.9% as against +0.2% respectively in the BMD in the lumbar spine; and +3.9% as against -1.2% in the BMD in the femoral neck. This means a statistically significant increase ($p<0.001$ for all comparisons) in BMD in the group treated with zoledronic acid of 6.02% in the total hip (CI 95%: 5.77 to 6.28), of 6.71% in the lumbar spine (CI 95%: 5.69 to 7.74) and 5.06% in the femoral neck (CI 95%: 4.75 to 5.36), in comparison with the placebo group.

In principle, these changes do not only reflect an increase in the density of the lumbar vertebral bodies, but also any change in the calcification of the aorta or the density of the posterior processes, none of which would contribute to the resistance of the vertebral body.

The evaluation of the spinal BMD by DEXA integrates the cortical and trabecular bone compartments with the limitation of including in the anteposterior projection the image of the posterior processes of the spine, or aortic calcifications if they exist. For this reason a sub-analysis of HORIZON-PFT was carried out in which, by means of quantitative computerised tomography (which defines with greater clarity the cortical and trabecular compartments) which found that zoledronic acid caused both an increase in total bone and an increase in spongy bone in the hip. The changes after three years of treatment were +2.9% against -3.2% for the placebo. However, the difference in changes in the cortical bone were not statistically significant (-0.4% as against -1.4% in the placebo group)[10]. The same was observed in the spinal column, where the results obtained by bone densitometry in HORIZON-PFT and by quantitative computerised tomography in this sub-study, were similar[11].

Another phase II clinical trial, randomised, double blind, placebo controlled, studied the effect of zoledronic acid at doses of 0.25, 0.5, and 1 mg as against a placebo in 351 postmenopausal women with low BMD[12]. After a year of the clinical trial it was observed that the increases in BMD in the spinal column in all the groups which had taken zoledronic acid (even at different doses) were similar. These were between 4.3% and 5.1% of the average BMD in the placebo group ($p<0.001$), and remained stable. The BMD in the femoral neck also increased progressively during the whole period of the study. While the BMD in the femoral neck of the placebo group decreased by 0.4%, if we compared this with the groups which took zoledronic acid, these groups had a significantly higher difference of between 3.1% and 5.1% with respect to the placebo group[10].

With regard to the markers for remodelled bone, in the clinical trial HORIZON-PFT it was also observed that the three biochemical markers diminished significantly in patients treated with zoledronic acid in comparison with those in the placebo group. At 12 months the blood concentrations of carboxy-terminal telopeptide of type 1 collagen, of bone-specific alkaline phosphatase and of amino-terminal propeptide of type 1 collagen had reduced by 59% (95% CI: 55 to 63), 30% (95% CI: 27 to 32) and 58% (95% CI: 55 to 60), respectively in the group treated with zoledronic acid ($p< 0.001$ for all the comparisons)[9].

Table 1. Relative risks of incidence of fracture in the two groups of the study. Horizon-PFT study[8]

Type of fracture	Placebo Nº of patients (%)	Zoledronic Acid Nº of patients (%)	Relative risk (IC del 95%)	P value
Morphometric vertebral fracture (stratum I)	310 (10.9)	92 (3.3)	0.30 (0.24-0.38)	p< 0.001
Hip fracture	88 (2.5)	52 (1.4)	0.59 (0.42-0.83)	p< 0.002
Non-vertebral fracture	388 (10.7)	292 (8.0)	0.75 (0.64-0.87)	p< 0.001
Any clinical fracture	456 (12.8)	308 (8.4)	0.67 (0.58-0.77)	p< 0.001
Clinical vertebral fracture	84 (2.6)	19 (0.5)	0.23 (0.14-0.37)	p< 0.001
Multiple (≥ 2) morphometric vertebral fractures (stratum I)	66 (2.3)	7 (0.2)	0.11 (0.05-0.23)	p< 0.001

III. Effects on histology and bone resistance

Long term treatment with zoledronic acid does not appear to affect bone quality in postmenopausal patients with osteoporosis. At the end of the HORIZON-PFT clinical trial no qualitative alterations were detected in bone tissue, in fibrosis of the medulla or in cellular toxicity in bone biopsies taken in patients participating in this study. In addition, quantitative histology revealed the preservation of trabecular bone architecture in biopsies taken from patients treated over three years with zoledronic acid.

Quantitative computerised tomographic data from patients in the HORIZON-PFT[11] study showed that zoledronic acid also improved some strength indices. After three years of treatment, the resistance to bone compression improved significantly (p≤ 0.001) in those patients who had taken zoledronic acid in relation to patients treated with a placebo[13]. The analysis carried out of the quantitative computerised tomographies showed an average change from the initiation of treatment with zoledronic acid and with a placebo of +4.9% as against -3.7% in the femoral neck, and of +9.8% as against -4.3% in the trochanter, respectively[11]. There was also an improvement in the volume of cortical bone with treatment with this biphosphonate. The average of the total variations in the hip from the point of initiation was 7.20%, as opposed to -0.02% with the placebo (p= 0.003).

b) In patients with hip fracture due to light trauma

The therapeutic efficacy of zoledronic acid in patients who have suffered a hip fracture due to light trauma has also been demonstrated in a multicentric, double blind, randomised trial of three years duration, known as the HORIZON-Recurrent Fracture Trial (HORIZON-RFT)[14]. 2,127 patients were studied over an average follow up period of 1.9 years.

This study included men and women over 50 years of age who had suffered a hip fracture as a consequence of a light trauma, and whose fracture had been treated surgically in the 90 days following the trauma. These patients had these characteristics in common: they had both legs, they had been tracked in the outpatient clinic before the fracture, and they did not want, or were unable, to receive treatment with oral biphosphonates. Excluded from the study were those patients treated with strontium or sodium fluoride, those who had a bone disease other than osteoporosis, those who suffered from cancer, and those who had a creatinine clearance lower than 30 mL/min (<1.8 L/h), blood calcium > 2.8 or < 2.0mmol/L or a life expectancy of less than six months. As in HORIZON-PFT[8], those patients who had been treated earlier with biphosphonates or PTH were subject to a cleansing period. Simultaneous treatments with modulators selective for oestrogen receptor, calcitonin, tibolon or hormonal therapy, and external hip protectors were permitted.

1,065 patients were randomly allocated to receive an intravenous infusion of 5 mg of zoledronic acid over 15 minutes and 1,062 to receive a placebo, annually. In this clinical trial all patients were also administered calcium and vitamin D.

The principle measure of efficacy in the study was the appearance of new fractures. Secondary measures of efficacy included new hip fracture, vertebral or non-vertebral fractures, and the change in BMD in the hip not fractured during the study.

After two years of treatment, the treatment with zoledronic acid reduced clinically the risk of new fractures by 35% compared with the placebo. While

13.9% of the patients who took the placebo suffered a clinical fracture during the two years of follow up, only 8.6% of those patients receiving zoledronic acid had a new fracture. The drug reduced significantly the risk of suffering a new non-vertebral fracture (7.6% of the beneficiaries of zoledronic acid as opposed to 10.6% of those taking the placebo) and vertebral fractures (1.7% as opposed to 3.8%, respectively) by 27% and 46% respectively compared with the placebo, $p< 0.05$ in all cases. In their turn, the BMD in total hip and in the femoral neck improved significantly ($p< 0.001$) with zoledronic acid compared with the placebo. After 12 months, the changes since the start of treatment were +2.6% in total hip and +0.8% in the femoral neck compared with -1.0% and -1.7% respectively for the placebo. After 24 months of follow up the figures were +4.7% and +2.2% compared with -0.7% and -2.1%, respectively. And finally, after 36 months of observation, +5.5% and +3.6% as compared with -0.9% and -0.7% respectively.

The conclusions of the study were that an intravenous infusion of 5 mg of zoledronic acid over 15 minutes significantly reduces the risk of suffering new fractures and results in an improvement in BMD, in men and women who have suffered a hip fracture after a light trauma. A surprising, but highly practical, finding is a reduction in mortality of 28% observed in the group of patients who received zoledronic acid.

A doubt has been raised as to what is the best moment for the administration of zoledronic acid after a hip fracture, since it has been suggested that this drug might interfere with physiological repair mechanisms, but this has not been demonstrated. Eriksen et al.[15] observed in a post-hoc analysis of the HORIZON-PFT study that the median period of time of the first infusion after surgical intervention was 46 days (range= 1 to 123 days) and found that the first infusion of 5 mg of zoledronic acid administered after the first two weeks from the surgical intervention was more efficacious in the reduction of risk of new fractures. The current trend in some services in Spain is to administer the infusion of zoledronic acid at two months from the surgical intervention. This is a subject which merits further debate.

Zoledronic acid compared with other drugs for the treatment of osteoporosis

a) Zoledronic acid against alendronate

The association between a low bone mineral density and the appearance of fractures is widely known[16]. However, only one in five patients who have suffered a fracture will follow on with a treatment for osteoporosis[17], and it is estimated that 20% of women who have suffered a vertebral fracture will present with another fracture within a year[18]. From this comes the importance that bone turnover is normalised rapidly in patients with high risk of fracture.

A multicentric trial of 24 weeks, randomised, double blind and with double placebo, showed that a single infusion of 5 mg of zoledronic acid took effect more rapidly than 70 mg of aledronate taken orally weekly in postmenopausal patients with low BMD[19]. This was found by comparing the relative change with respect to the baseline situation of the marker for bone resorption urinary N-telopeptide of type 1 collagen (NTX) after the first week in both groups, and by observing that the treatment with zoledronic acid produced a reduction significantly greater than that of oral alendronate. In addition, during the 24 weeks which the study lasted, the reductions in NTX were higher at all moments of post-baseline evaluation in the group treated with zoledronic acid, with concentrations of NTX which stayed at premenopausal values from week 12 to the end of the study. It is important to point out that significant reductions in NTX are not solely associated with a reduction in bone resorption, but also, in postmenopausal women with osteopenia or without osteoporosis, reductions in NTX at three months are closely associated with increases in BMD in the lumbar spine at one year[20]. The concentrations of bone-specific alkaline phosphatase (BSAP), marker for bone formation, showed a more gradual reduction in both the group which received 5 mg of zoledronic acid, and in that which received 70 mg weekly of alendronate orally, reaching the margin of premenopausal values at week 12.

In a co-operative, multicentric, randomised double blind non-inferiority study, Orwoll et al.[21] evaluated in 302 men affected by osteoporosis the effect of 5 mg i.v. annually of zoledronic acid as against 70 mg weekly of aledronate. Bone mineral density and biochemical markers for bone remodelling were studied and it was observed that after 24 months the results were equivalent in all the parameters analysed, but that the men preferred the annual i.v. administration of zoledronic acid.

A controversial aspect of treatment for postmenopausal osteoporosis is the excessive suppression of bone turnover. However, data from this study show that a rapid reduction in the markers for bone resorption are followed by a slow but continous increase in concentrations over the following six months. On the other hand, histological studies 13 have allowed the rejection of the existence of “frozen bone”, a syndrome widely feared in patients taking biphosphonates with a hypothetical excess of suppression of remodelling.

Adverse effects were more frequent in the group which took zoledronic acid than in those taking alendronate (91% for the group on 5 mg of zoledronic acid intravenously compared with 86.4% for 70 mg of alendronate orally). However these symptoms were mostly flu-like and disappeared after the first three days from the administration of the drug.

Finally, when patients were asked for their preferred treatment, most of them went for the annual intravenous treatment due to its greater ease of use, higher satisfaction and wider availability as a treatment to be taken over a prolonged period. This point will be commented on at greater length below.

b) Comparison with other drugs

Jansen et al.[22] conducted a study to compare the efficacy of the biphosphonates in the reduction of risk of vertebral fracture in women affected by postmenopausal osteoporosis. To achieve this, after a systematic literature search, they analysed the baseline results in patients included in different studies. The results of this work suggest that there is a 98% probability that, among the 4 biphosphonates studied, zoledronic acid shows a greater reduction in the risk of vertebral fractures.

Zoledronic acid in patients with osteoporosis induced by glucocorticoids.

Due to their anti-inflammatory and immunosuppressive effects, the use of glucocorticoids in clinical practice is very extensive, and their effectiveness undisputed. However, their chronic use carries the risk of producing many adverse effects, of which osteoporosis is one of the most frequent and concerning[23,24]. Treatment with glucocorticoids are associated with a higher loss of bone mass and, therefore, a higher risk of suffering a fracture in the future.

An annual induction of 5 mg of zoledronic acid has been authorised in the European Union to treat men and women with osteoporosis caused by the chronic and continual use in low doses of glucocorticoids (usually known as steroids). In a randomised, double blind study of a year's duration, conducted in 54 centres in 12 European countries, Australia, Hong Kong, Israel and the US, it was observed that the efficacy of an infusion of 5 mg of zoledronic acid was greater than 5 mg of risedronate orally, daily, for the prevention and treatment of osteoporosis induced by glucocorticoids[25]. 833 patients were randomly allocated to receive either zoledronic acid (n=416) or risedronate (n=417). The patients were grouped by sex, and assigned to treatment or prevention subgroups, depending on the duration of their use of glucocorticoids which they had been taking before the study. The treatment sub-group consisted of patients treated for more than 3 months (272 patients receiving zoledronic acid and 273 risedronate), and the prevention sub-group consisted of patients treated for less than 3 months (144 patients for each biphosphonate). The results of this clinical trial were that, after 12 months, the increases in bone mineral density in the lumbar spine were significantly higher for those on zoledronic acid than for those on risedronate, in both the prevention and treatment sub-groups. In turn, after 6 months of the study, the zoledronic acid produced a significantly higher, and earlier, increase in BMD than risedronate, indicating a more rapid start to its efficacy. Although once again the adverse effects were more frequent in those patients who received zoledronic acid, again, they were light, occurring during the first three days after the infusion and were quickly controlled. The more serious adverse events were a worsening of rheumatoid arthritis in the treatment subgroup, and fever in the prevention sub-group.

In conclusion, therapy with zoledronic acid is more effective, and with a quicker action, than the current established therapy for the treatment of osteoporosis induced by glucocorticoids, having also the advantage of proper annual compliance and of providing sustained osteo-protection[25].

Zoledronic acid in male osteoporosis

It is estimated that one in five men over 50 years of age will suffer a fracture due to osteoporosis. Zoledronic acid has recently been approved by the European Union for the treatment of osteoporosis in men who have a high risk of fracture, so improving the quality of life of this section of the population. These conclusions have been reached as a result of the HORIZON-Recurrent Fracture Trial which was commented on in more detail in the section on the benefits of zoledronic acid in patients who have suffered a hip fracture due to light trauma[26]. In fact, zoledronic acid is one of the few drugs accepted in Spain for the treatment of osteoporosis in males.

Preferences for treatment

As we have already mentioned, the oral biphosphonates increase bone mineral density and reduce the frequency of vertebral fractures, but they have had, as limitations, poor absorption, adverse effects on the digestive tract, and difficulties in taking the treatment. In addition, they are associated with poor compliance and low therapeutic adherence. Many patients to whom these antiosteoporotic drugs are prescribed abandon the treatment and, after 12 months, the majority take less than 80% of the pills prescribed[27-30]. This poor adherence to oral biphosphonates compromises their efficacy in reducing fractures and increases medical costs[31,32], above all in older disabled adults, who often cannot follow the administration regime properly and strictly[33].

Weekly treatments provide a better adherence than daily treatments, but even so, a sufficient adherence is only reached in around 50% of patients[27,30]. For this reason, a regime of administration of an annual perfusion guarantees to patients a full therapeutic effect for at least 12 months. This has been observed in a study which compared the efficacy of a single annual infusion of zoledronic acid, as against that of alendronate, taken orally weekly, in postmenopausal patients with low bone mineral density[19]. In this study, all patients who had taken medication or placebo intravenously, or orally weekly, were asked if they preferred the annual intravenous infusion, weekly oral treatment, or both equally. Of the 221 patients of all categories evaluated who had responded to the questionnaire, 73.8% expressed a general preference for annual intravenous infusions, 9% preferred weekly oral administration, while 11.8% considered both dosage regimes as equal[34].

A regime of administration once a year is an attractive option for the treatment of osteoporosis since it will provide assured bone protection over the whole year. In addition, as has already been

mentioned, the intravenous administration results in a quicker initiation of activity than that obtained with oral biphosphonates[19].

Tolerability

In general, if we compare the tolerability of patients to zoledronic acid as against a placebo, this has been good[23,24]. Although it is true that the number of adverse effects in the group which took zoledronic acid was higher than that of the placebo, these effects were mostly light and transitory. While in the HORIZON-PTF study the incidence of adverse effects was 95.5% and 93.9% respectively, with a p-value significantly equal at 0.002, in HORIZON-RFT no statistically significant difference was found between the two groups. However, in HORIZON-PTF there were no significant differences in terms of the incidence of serious adverse effects or the abandonment of the study by patients (29.2% as against 31.1% and 38.3% as against 41.2%, respectively).

The most frequent symptoms were reported in the three days following the perfusion of the medicine. These were pyrexia, flu-like symptoms, myalgia, headache and arthralgia. In general these symptoms were classified as light or moderate and dissipated over a period of 3 days. The proportion of patients who received zoledronic acid and who in turn had some post-administration symptom was significantly higher compared with the placebo group after the first day (31.6% as against 6.2%), the second day (6.6% as against 2.1%), and after the third day (2.8% as against 1.1%). It is important to note that in patients from the HORIZON-RFT study who received paracetamol at the time of, and after, the perfusion of the treatment, only the mylagia and pyrexia were significantly higher in the group which received the zoledronic acid[14].

An annual therapy with zoledronic acid is not associated with renal toxicity in the long term. Although between days 9 and 11 after the perfusion 1.3% of the patients in the group treated with zoledronic acid presented an increase of more than 0.5 mg/dl in the blood concentration of creatinine, as opposed to 0.4% of patients in the placebo group, these changes were transitory; by the end of 30 days, in more than 85% of patients, the concentrations had returned to being within a margin of 0.5 mg/dl with respect to the values before the perfusion and in the remainder, they had returned to these levels by the following annual review. After three years of treatment no significant differences were observed between the taking of the placebo or the zoledronic acid in terms of the concentrations of blood creatinine or in creatinine clearance[13,14].

In addition, although after 9-11 days from the first perfusion, 49 patients from the group treated with zoledronic acid had blood calcium lower than 2,075 mmol/l, compared with 1 patient in the placebo group, all these events were transitory and asymptomatic.

Generally, the cardiovascular tolerability was similar in the patients of both groups. However, 6.9% of those patients treated with zoledronic acid presented with arrhythmia, and this was significantly higher (p=0.003) than in the placebo group in which 5.3% of patients developed it. While in HORIZON-RFT no notable difference was found in the incidence of serious arrhythmia (1.1% as against 1.3% in patients in the zoledronic acid group and in the placebo group, respectively), it is important to note that the incidence of auricular fibrillation in HORIZON-PFT was indeed significantly higher in the group treated with the biphosphonate compared to that with the placebo (1.3% as against 0.5% respectively, with a p-value of <0.001). However, after the evaluation, the number of patients whose auricular fibrillation was reported as a serious event hardly varied (50 in the group treated with zoledronic acid and 17 in the placebo group). Subsequently, various meta-analyses have confirmed that there is no association between the use of biphosphonates and auricular fibrillation[35-39].

It is well known that most of the cases of maxillary osteonecrosis have been observed in patients with cancer treated with frequent and high doses of intravenous biphosphonates[40-42]. However, in the HORIZON-PFT reference study there were no spontaneous notifications of mandibular osteonecrosis. By means of a search of a database of adverse events in the trial, which was followed by an evaluation by experts, two possible cases of maxillary osteonecrosis were identified (one in the placebo group and one in the group treated with zoledronic acid). In both patients, this resulted in a delay in healing after surgery, and the two cases were resolved later with antibiotic and debridement treatment[8,14]. Four patients who received zoledronic acid developed osteonecrosis in the knee or hip, compared with three patients in the placebo group[8]. Hence, a SEIOMM position document produced in conjunction with all the national societies dedicated to osteoporosis and all the odontological and/or maxillofacial societies, established that zoledronic acid utilised at doses which are used in the treatment of osteoporosis does not increase the risk of maxillary osteonecrosis[43].

Finally, a slight increase in the risk of adverse inflammatory opthalmological events in the 15 days following the perfusion was confirmed 8, as has been noted in relation to other biphosphonates. However, these events were treated and resolved with outpatient treatment in all cases.

Recommendations on dose and method of administration

Zoledronic acid received the approval of the regulatory authorities of the US (FDA) and the European Union (EMEA) as the first and only once-yearly treatment for women with postmenopausal osteoporosis.

In the European Union and in the United States, the use of zoledronic acid has been approved as a treatment for osteoporosis in postmenopausal women at risk of fracture. It has also been

approved for patients who have suffered a hip fracture through trauma, and in Europe, in men who suffer from osteoporosis and who have a high risk of suffering a fracture. 5 mg of intravenous zoledronic acid annual is recommended, administered in a single infusion of 100 ml over a minimum period of 15 minutes. Before the infusion, it is recommended that the blood levels of calcium are established and that a calculation of creatinine clearance be carried out by determining the levels of blood creatinine. Also, it is necessary to confirm the prior state hydration of the patient and advise them to drink at least two glasses of water before the infusion, and continue after it with normal hydration. A supplement of calcium and vitamin D is also recommended.

In patients older than 65 years of age, or with light to moderate renal deficiency, it is not necessary to adjust the dose of zoledronic acid. In the European Union, neither is such an adjustment in dosage recommended in patients who suffer liver insufficiency, but this is not the case in the United States. Finally, treatment with this third generation biphosphonate is not recommended in patients suffering from serious renal insufficiency (creatinine clearance < 35 mL/min).

The Spanish Society for Bone and Mineral Metabolism Research (SEIOMM), in the update of its guides for the treatment of postmenopausal, steroidal and male osteoporosis, recommends the consideration of zoledronic acid as a drug with a grade of recommendation A for the reduction of osteoporotic vertebral, non-vertebral and hip fractures[2].

Zoledronic acid as a preventative treatment

Every day more articles are being published which demonstrate the efficacy of zoledronic acid in the prevention of bone loss in patients.

A study published recently demonstrated that treatment every three months with zoledronic acid over a year, was efficacious against the loss of bone mass during the first year of chemotherapy in premenopausal women with breast cancer[44]. It is important to mention that adjuvant chemotherapy is associated with a significant reduction in bone mineral density in premenopausal women with breast cancer, hence the importance of a treatment efficacious in combating this.

In this study, 101 women were randomly assigned, 85 completed 12 months and 62 completed evaluations over the following 24 months. In the placebo group the blood C-telopeptide (CTX) increased progressively during the first 12 months, regressed towards the baseline, but stayed significantly above the line after 24 months. In the lumbar spine, the BMD diminished from the baseline value by 5.5% at 12 months, and by 6.3% at 24 months. Similarly, after 24 months, the BMD in the total hip and the femoral neck diminished by 2.6% and 2.4% respectively. However, in those patients who took zoledronate, the BMD remained stable ($p< 0.0001$ in comparison with the placebo). Although the blood CTX reduced significantly at 6 months, these levels returned to baseline levels at 12 months, remaining stable during the following 24 months.

There are also studies which try to establish the role of zoledronic acid in the prevention of loss of BMD in postmenopausal women. One example is the study carried out by McLung et al. whose objective was to evaluate the efficacy of zoledronic acid for the prevention of bone loss in postmenopausal women with low bone mass[45]. This clinical trial of two year duration, randomised, multicentric, double blind and placebo controlled, postmenopausal women with low bone mass were randomly selected to receive 5 mg of zoledronic acid intravenously at the time of their selection and at month 12 (two doses of 5 mg of zoledronic acid intravenously each year), 5 mg of zoledronic acid intravenously only at the time of selection and a placebo at month 12, or placebo at the time of random selection and at month 12.

The trial's results show that both in the group which received two doses of zoledronic acid annually, and that which received one dose, a statistically significant higher increase in BMD in the lumbar spine was produced in comparison with the group which received the placebo (5.58% and 4.42% in comparison with 1.32%, respectively, $P< 0.001$). Similarly, a statistically significantly greater increase in the BMD of the hip, femoral neck and trocanter was obtained in month 12 and month 24 (all with a p value < 0.001). Finally, in those patients who received zoledronic acid a statistically significant increase in markers for bone turnover was produced, although the changes in the group which received two one doses annually were greater. The total incidence of adverse events and of serious adverse effects were similar in all the treatment groups.

Cost-benefit

Osteoporosis places considerable economic demands on health resources[46-48]. It is for this reason that pharmaco-economic considerations are important factors in the selection of antiosteoporotic treatment. At present, the price of zoledronic acid is not high in comparison with other drugs. One infusion of zoledronic acid costs 422,65 € (Price plus VAT) in Spain. In Table 2 we can see the annual cost of zoledronic acid in comparison with other drugs used in the treatment of osteoporosis.

Conclusion

The intravenous administration of 5 mg of zoledronic acid once a year has been shown to be efficacious in the reduction of risk of vertebral fractures in patients with postmenopausal osteoporosis or hip fractures due to light trauma. It also produces an increase in bone mineral density and reductions in the markers for bone turnover, and is generally well tolerated. All this makes zoledronic acid a drug of first choice in the treatment of osteoporosis.

Table 2. Annual cost of different drugs used in the treatment of osteoporosis. Own development from the database of the General Council of the Official College of Pharmacologists. Version 198, (7-9-2010)

Active principal	Commercial name	Dose. Period. Method of administration	Presentation	Packet cost 28 days (Euros without VAT)	Annual cost (Euros without VAT)*
Zoledronic acid	Aclasta	5 mg. Annual i.v.	Bottle 100 ml	406.39	406.39**
Alendronate	Fosamax	70 mg. Weekly. Oral	Tablets. Packages with 4	21.19	275.47
Alendronate	Several generics	70 mg. Weekly. Oral	Tablets. Packages with 4	15.42	200.46
Alendronate + Vitamin D	Fosavance	70 mg. Weekly. Oral	Tablets. Packages with 4	27.47	357.11
Risedronate weekly	Acrel. Actonel	35 mg. Weekly. Oral	Tablets. Packages with 4	33.34	433.42
Risedronate weekly	Generics	35 mg. Weekly. Oral	Tablets. Packages with 4	22.93	298.09
Risedronate monthly	Acrel. Actonel	75 mg. Monthly 2 day. Oral	Tablets. Packages with 2	33.32	399.84
Ibandronate	Bonviva. Bondenza	150 mg. Monthly. Oral	Tablets. Packages with 1	33.32	399.84
Strontium ranelate	Protelos. Osseor	2 g. Diaily. Oral	Envelopes. Packages with 28	47.49	617.37
PTH 1-34	Forsteo	20 µg. Daily. Sub-cutaneous	Preloaded pen. Packages with 28 dose	384.79	5,002.87
PTH 1-84	Preotact	100 µg. Diaria. Sub-cutaneous	2 cartridges 14 dose c/u	380,95	4,952.35
Raloxifen	Evista. Optruma	60 mg. Diaily. Oral	Tablets. Packages with 28	33.08	430.04
Nasal calcitonin	Miacalcic. Several	200 UI. Daily. Nasal	Nebulizer Packages with 28 dose	72.13	937.69

*Calculated on the basis of 13 packets per year, since it should be taken into account that the tablets in packets of 28 provide 28*12 months=336 tablets per year. More than one additional packet is necessary (29 tablets) to complete 365 days of the year, with the exception of ibandronate.
**In the case of zoledronic acid the cost of 1 syringe, needle and 100ml saline solutions should be added, plus the cost of staff of day hospital or place where it is administered, which varies from one hospital centre to another.

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