Committee of Experts of SEIOMM for the production of the guides
(See Annex 1)

Clinical Practice Guidelines for Posmenopausal, Esteroid and Male Osteoporosis

Introduction

When the last version of the "Clinical Practice Guidelines for Posmenopausal, Esteroid and Male Osteoporosis", Society of Bone and Mineral Metabolism Research[1] was produced it was agreed that it should be revised at least every 5-6 years, by editing a new version of the same document. At an intermediate point –at around 2-3 years– an update should have been produced, to include issues which could not wait for the editing of the new version, especially taking into account the fact that even as the second version was written the introduction to market of the new drugs was already being foreseen. The following document includes this update. It should be stressed that this should not be treated as an entire revision of the guides, rather only of some aspects –fundamentally therapeutic issues– considered most urgent.

Given that this should not be treated as a complete revision of the guides, rather only its update, we have considered it proper to take into account solely information relevant from the practical point of view; specifically, information related to the efficacy of the drugs in reducing the incidence of fractures. We have not assessed data related to substituted variables, such as Bone Mineral Density (BMD) or markers for bone turnover. However, we have included comparative studies or non-inferiority studies regularly carried out with BMD as a variable of efficacy, given that they definitely constitute an indirect way of establishing the usefulness of a particular drug –or in a particular way of administering them– for fractures.

Methodology

A systematic search of the bibliography in PubMed was carried out, with two different approaches: a) a search under "Theraputics", of the "Clinical Enquiries" section, using the names of the various drugs; b) a search starting with the MeSH terms, using the names of the various drugs, plus the terms "fracture" or "osteoporosis". The names of the drugs used in the searches were the following: etidronate, alendronate, risedronate, ibandronate, zoledronate, strontium ranelate, oestrogens, hormone replacement therapy, raloxifene, tibolone, calcitonin, PTH, parathormone, PTH 1-34, teriparatide, PTH 1-84, fluoride. The period of the bibliographic search started in January 2006, the point at which the systematic search for the second version of the guides ceased, and ended in December 2008. In addition to the works found in the systematic search over the aforementioned period, we also considered for this update information based on personal knowledge gained through regular handling of the bibliography related to this subject, and data presented at conferences; this information was included even though it was collected after the systematic search had been completed.

In order to assess efficacy in relation to fractures we analysed only works designed as clinical trials or meta-analyses, rejecting observational studies.

A first draft was written by the co-ordinator of guides (JGM), which was distributed among all the members of the Committee of Experts of the SEIOMM charged with producing the second version. They proposed changes to the document, according to which a second draft was produced, which again was sent to the members of the Committee. Finally, with the comments on this second draft the final, definitive version was produced, which was approved by the Committee. The document was submitted for the consideration of the scientific societies interested in osteoporosis.

Works selected

Postmenopausal osteoporosis

From the initial assessment of the works provided through the aforementioned bibliographic search, we considered of interest for inclusion in the current update the following: two non-inferiority studies of risedronate administered monthly[2,3], two meta-analyses of ibandronate[4,5] two clinical trials with zoledronate[6,7], a clinical trial of tibolone[8], another clinical trial of PTH 1-84[9], and three studies of strontium ranelate[10–12], the prolongation of SOTI[13] and of TROPOS[14].

With the desire to offer the most complete information, we have also included in this document works carried out with some drugs which are not yet approved for use in the treatment of osteoporosis, but of which there is data (published or communicated at conferences) on their efficacy in reducing osteoporotic fractures. For this reason we make reference to two clinical trials of both of the new SERM (bazedoxifene[15]) and another of denosumab[16], and a meta-analysis of fluoride[17].

1. Risedronate

The two non-inferiority studies published on risedronate administered monthly differ exclusively in the way the drug is administered: in one trial 75 mg. is administered in two consecutive days, while in the other 150 mg. is given in a single day.

1.1 Non-inferiority study which compares the effect of 75 mg. of risedronate administered on two consecutive days, once a month (150 mg. monthly) with that of 5 mg. daily[2].

This trial was carried out with 1229 women with postmenopausal osteoporosis, its principal objective being the assessment of changes in BMD in the lumbar spinal column over 12 months. The limit of the margin of non-inferiority was established at -1.5%. The group treated on the daily model increased its BMD by 3.6%, while in the group treated monthly the increase was 3.4%. The limits of the interval of confidence in the differences at 95% were -0.189 and 0.618%, in such a way that all the points of the aforementioned interval were found within the margin of non-inferiority.

1.2 Non-inferiority study which compares the effect of 150 mg. of risedronate administered one a single day per month, with that of 5 mg. daily[3].

This study is practically superimposable on the previous study, with the difference being in the monthly model for the administration of risedronate (150 mg. in a single day, instead of in two consecutive days). The number of women with postmenopausal osteoporosis included was 1094. The limit of the margin of non-inferiority was also established at -1.5%. The group treated on a daily basis increased its BMD in the lumbar spinal column by 3.4%, while in those treated monthly this increased by 3.5%. The limits of the interval of confidence in the differences at 95% were from -0.51 to 0.27%. So, in this case also, all the points of the aforementioned interval were found within the margin of non-inferiority.

Both trials have a level of evidence 1b, and in view of them the monthly theraputic regimen can be considered to be acceptable for risedronate (grade of recommendation, A).

2. Ibandronate

Two meta-analyses of the use of ibandronate have appeared, characterised by the use of the concept of an "accumulated drug dose" for those patients included in the trials at the end of a year of treatment. In those trials in which the drug was administered intravenously, the accumulated dose was considered to be the total administered by the end of one year. In the trials in which the drug was administered orally, the accumulated dose was considered to be 0.6% of the total dose administered over the same period. The two meta-analyses differed fundamentally in that the first[4] used historic controls, while the second one[5] did not. On the other hand, what they had in common was that in both cases the principal objective is non-vertebral fractures, and that these fractures were frequently picked up as adverse effects.

2.1 First meta-analysis

The patients in this first meta-analysis[4] could belong to four groups, depending on the quantity of the drug accumulated per year: a) ≥ 10.8 mg; b) 5.5-7.2 mg; c) 2.0-4.0 mg; d) 0 mg (placebo group). The outcome variables were: a) the main non-vertebral fractures (clavicle, humerus, wrist, pelvis, hip, leg); b) all non-vertebral fractures; c) all clinical fractures. The main results are derived from the comparison of the first (≥ 10.8 mg) and last (placebo) groups. The reduction in risk of the first type of fracture in the group with a total accumulate dose ≥ 10.8 mg. with respect to the placebo group was 34.4% (p = 0.032), that of the second group 29.9% (p = 0.041) and of the third group 28.8% (p = 0.010). The most important methodological limitation of this meta-analysis is that the patients assigned to the placebo group pertained to a different study from those in whom the accumulated dose was ≥ 10.8 mg. for which reason it should definitely be treated as a study with historic controls. On the other hand, the non-vertebral fractures were noted as adverse effects in half of the studies included in the meta-analysis. It being difficult to establish a firm grade of evidence for this work, we believe that in any case, in itself, it does not merit a grade of recommendation higher than C.

2.2. Second meta-analysis

The fundamental difference with the previous meta-analysis[4] is that in this one[5] the point of reference is not the placebo, but rather a daily dose of 2.5 mg. In the end, to avoid the historical character of the controls, the authors compare pairs of patients belonging to the same study. The study includes a greater number of trials. The principal outcome variables are the main non-vertebral fractures. In the main analysis comparison has been made between those patients with the highest accumulation of drugs (≥ 10.8 mg) and those with the lowest (5.5.mg). Another comparison was made

between those with the highest amounts and, those with the lowest and intermediate amounts combined. The accumulated dose of 10.8 mg or more corresponds to the combination of studies with 2 or 3 mg intravenously every 2 or 3 months (respectively), and with 150 mg. orally per month. The incidence of non-vertebral fractures is significantly less in the group with an accumulated dose of ≥ 10.8 mg than in that with an accumulated dose of 5.5 mg, with a hazard ratio (HR) of 0.621 (0.396-0.974). The result is similar if the high dose is compared with the combination of the low and the medium doses. Although this is a much more consistent work than the previous one, it retains the limitation that it supposes that the fractures are gathered as adverse effects. In fact the authors of the work themselves indicate that while the results are consistent with the idea that ibandronate is efficacious in the reduction of non-vertebral fractures, it does not provide the same level of evidence as a clinical trial, for which reason the level of evidence, in the best of cases, can not be more than 2a.

In the face of this meta-analysis, we conclude that a recommendation B can be given to ibandronate in as much as it refers to the diminution of non-vertebral fractures.

3. Zoledronate

Zoledronate has already been mentioned in the second version of the guides, but that was not considered to be the final assessment – neither was the algorithm included since the results of the pivotal study of women with postmenopausal osteoporosis (HORIZON-PFT)[6] had not yet been published. Here we comment on this work, together with another which included men and women, and which was carried out in patients with a fracture of the hip (HORIZON-RFT)[7]. This second study, therefore, does not strictly refer to postmenopausal osteoporosis, but rather to senile osteoporosis.

3.1 Pivotal study

This deals with a study[6] carried out in postmenopausal women with osteoporosis, and it is designed as a randomized, double blind, placebo controlled clinical trial. It was carried out with 7765 women with BMD ≤ -2.5 or ≤ -1.5 plus a moderate vertebral fracture or two light vertebral fractures. 21% of the patients was following treatment with other antiosteoporotic drugs distinct from the biphosphonates or PTH, such as sex hormones, raloxifene or calcitonin. The study lasted for 3 years and the patients were assigned either to the placebo or to 5 mg of zoledronate, i.v., annually. The primary objective was twofold: differences in the incidence of new vertebral fractures in patients who did not follow other concomitant antiosteoporotic treatment, and differences in the incidence of hip fractures in all patients. The secondary objectives were the development of other types of fractures (non-vertebral fractures, whichever clinical fractures, clinical vertebral fractures), changes in BMD (lumbar spinal column, femoral neck, the whole hip) and changes in the markers for bone turnover (CTX, bone alkaline phosphatase and PINP), as well as security data. The relative risk (RR) of morphometric vertebral fractures after three years was 0.30 (0.24-0.38). In the case of hip fractures the HR was 0.59 (0.42-0.83). Hence, with reference to non-vertebral fractures, the HR was 0.75 (0.64-0.87), in the combination of clinical fractures it was 0.67 (0.58-0.77), and in clinical vertebral fractures it was 0.23 (0.14-0.387). With respect to the adverse effects, important note should be taken of a higher incidence of what the authors named "serious auricular fibrillation" in the group treated with zoledronate (2.5% vs.1%, p<0,001). Together with this, and as is known from patients administered biphosphonates intravenously, patients assigned zoledronate presented a clinical picture of "pseudoinfluenza" or an "acute reaction phase", which affected approximately 30% of the population after the first injection, and at lower percentages at subsequent injections (around 6% at the second and 2% at the third).

3.2 Refracture study

This study[7] was carried out in patients of both sexes with a previous hip fracture. From the outset, it was designed to be randomised, double blind, and placebo controlled. On this occasion the study was carried out with 2127 patients (ratio of women to men – 75:25), they were followed for an average of 1.9 years. It was intended to continue the study until reaching fracture 211.The patients were assigned a placebo or 5 mg of zoladronate, i.v., annually. Their inclusion in the study took place within 3 months of surgical intervention. The primary objective was the appearance of new clinical fractures (excluding those in the face or the fingers). The secondary objectives were the appearance of new clinical vertebral and non-vertebral fractures, and fractures of the hip, as well as contralateral changes in the BMD of the hip, and security data previously established (including among them, mortality). The HR of all the new clinical fractures was 0.65 (0.50-0.84), that of the non-vertebral fractures 0.73 (0.55-0.98), that of the clinical vertebral fractures 0.54 (0.32-0.92), and that of the hip fractures 0.70 (0.41-1.19). In this trial no increase in auricular fibrillation in the patients treated with zoledronate was observed, however a beneficial effect of particular interest was detected: a reduction of 28% globally in mortality (from whatever cause) in the group assigned to zoledronate (p = 0.01). Logically, also observed were the manifestations of pseudo-influenza associated with intravenous biphosphonates, although in this case the incidence was significantly low (something less than 7% with the first injection and 0.5-1% with subsequent injections).

A *post hoc* analysis of this work[19] has studied whether the time elapsed from the suffering of the fracture to the administration of the drug can influence its effect. The results suggest that the drug is most efficacious if administered after two weeks because maybe if it is done earlier the drug tends to accumulate in the callous of the fracture.

Neither of the two trials spontaneously reported cases of osteonecrosis of the jaw bone. One earlier search directed especially at the detection of this complication in the pivotal study, signalled the possibility that there might be a case in each group.

Both trials have a level of evidence of 1b, which allows the assignation to zoledronate of the grade of recommendation A for the reduction of vertebral, non-vertebral and hip osteoporotic fractures.

4. Tibolone

A randomised, double blind, placebo controlled clinical trial has been carried out on tibolone[8] which included 4538 women from 65 to 85 years of age, either with BMD ≤-2.5 T in the hip or lumbar spinal column, or with BMD ≤-2.0 T plus vertebral fracture. They were assigned 1.5 mg of tibolone daily or a placebo. The primary objective was the appearance of new vertebral fractures, and the secondary objective the incidence of non-vertebral fractures, breast cancer, venous thrombosis or vascular disease. The study was interrupted at 34 months because of the appearance of serious secondary effects (ictus). The results can be summarised in the following way: HR of vertebral fracture, 0.55 (0.41-0.74]); HR of non-vertebral fracture, 0.74 (0.58-0.93); HR of invasive breast cancer, 0.32 (0.13-0.80); HR of cancer of the colon, 0.31 (0.10-0.96); HR de ictus, 2.19 (1.14-4.23). The authors' conclusion is that tibolone reduces the risk of vertebral or non-vertebral fracture, of breast cancer and possibly cancer of the colon, but increases the risk of ictus in older women.

The level of evidence in the trial is 1b, and as a result of this evidence we would discourage the use of tibolone in the treatment of osteoporosis in older women (> 65 years) and in women with risk of ictus (grade of recommendation A).

5. PTH 1-84

As we also commented on zoledronate, PTH 1-84 was already mentioned in the second version of the guides, but this was not considered as a final assessment because the results of the pivotal study[9] had not yet been published, nor had it been approved for commercial use. What follows is a more detailed account of this study.

It consisted of a randomised, double blind placebo controlled clinical trial which involved 2532 postmenopausal women who complied with one of the following criteria: A/ aged 45-54 years and I) BMD ≤ -3 T in the lumbar spinal column femoral neck or the whole hip, without vertebral fractures or II) BMD ≤ -2.5 T and 1-4 previous vertebral fractures; B/ aged ≥ 55 years and I) BMD ≤ -2.5 T without vertebral fractures, or II) BMD ≤ -2.0 T and 1-4 previous vertebral fractures. Approximately 19% of the patients presented with at least one vertebral fracture at the time they were included. The patients were assigned 100mg/d. of PTH 1-84 administered subcutaneously, or a placebo, for 18 months. The principal objective of the study was the appearance of new vertebral fractures and changes in the BMD. The RR for new vertebral fracture was 0.42 (0.24-0.72) and for non-vertebral fracture 0.97 (0.71-1.33). The percentage of women included in intention to treat analysis was 67.2%.

The level of evidence is 1b with a grade of recommendation A for the reduction of vertebral fractures.

6. Strontium ranelate

The results after 5 years[10] of the TROPOS study, whose results after 3 years[14] were already commented upon in the second version of the Guides, and whose principal objective was to study the effect of the drug on non-vertebral fractures, have been published. It was carried out as a randomised, double blind clinical trial in 5091 women who had been assigned 2g/d of strontium ranelate or a placebo over 5 years. At 3 years the RR of non-vertebral fractures had been reduced by 16%. A post hoc analysis carried out in women of 74 or more years with BMD in the femoral neck equal to or less than -2.4 T (reference: population NHANES III) showed a reduction of 36%. Vertebral fractures were reduced by 39%. The analysis at 5 years was planned in advance following the protocol. The number of women included in the intention to treat analysis was 97% of those originally included in the study, although the percentage who completed it was 53%. Those who were lost divided in a similar way in the two groups. The RR for non-vertebral fractures was 0.85 (0.73-0.99) and for the vertebral fractures, 0.76 (0.65-0.88). The post hoc analysis to assess the effect on hip fracture in high risk women showed an RR or 0.57 (0.33-0.97). The security profile of strontium ranelate was similar to those of the 3 year study.

There has also been published the results after 4 years[12] of the SOTI study[13], whose principal objective was to study the effect of strontium ranelate on vertebral fractures, and whose results after 3 years were also commented on in the previous version of the Guides. It consisted of a randomised, double blind, placebo controlled clinical trial carried out in 1649 postmenopausal women with at least one vertebral fracture. The group assigned to the treatment received 2g/d of strontium ranelate. At 3 years the RR for vertebral fractures had been reduced by 49%. The work on which we are now commenting presents the results of reduction in fractures at the fourth year. The intention to treat analysis included 87.6% of the women, with those lost at the end of the study at 30%. The RR for vertebral fractures was 0.67 (0.55-0.81). The RR for peripheric fractures was 0.92 (0.72-1.19). The original design of the study included an additional analysis at 5 years, after which half the women in the group having treatment moved to receiving the placebo, and all those receiving the placebo, received the treatment, but, this analysis at the fifth year was not intended to provide data regarding efficacy in fractures, but regarding the evolution of BMD.

Finally, data has been presented from a study[11] which analyses the effects of prolonging the ingestion of strontium ranelate over three years –in an open regimen– in women who had received the drug over 5 years in the SOTI or TROPOS studies[10,12]. The data refer exclusively to patients treated with strontium ranelate over 8 years, without there being a placebo group (all were treated from the start of the aforementioned studies, for four or five years). What is assessed in this work is the incidence of vertebral or non-vertebral fractures over these three years of prolongation, comparing it with their incidence during the first three years the patients were followed (that is, during the SOTI and TROPOS studies). The authors did not find significant differences, and concluded that this suggests that strontium ranelate maintains its efficacy in relation to both types of fracture over 8 years. The values for the incidence of the said fractures in both periods were as follows: for vertebral fractures, 13.7% for the last 3 years and 11.5% for the first 3; for non-vertebral fractures, 12.0% for the last 3 years and 9.6 for the first 3. The drug was tolerated well.

In conclusion data has been presented which indicates that strontium ranelate maintains its efficacy in relation to vertebral fracture for at least 4 years, and for non-vertebral fractures, for at least 5. There are, in addition, data which suggest that this happens over a longer period (8 years). A *post hoc* analysis with respect to hip fracture carried out after 5 years of treatment indicates results similar to those observed after 3 years. The results of these works while providing valid information with respect to the duration of the effectiveness of the drug, do not change the recommendations of these Guides in this respect, for which reason a recommendation A is retained in relation to vertebral and non-vertebral fractures, and B with respect to hip fractures.

7. Bazedoxifene

Bazedoxifene has been studied in a randomised, double blind, placebo controlled clinical trial[15], which included 6847 postmenopausal women with osteoporosis, assigned 20 or 40 mg/d. of bazedoxifene, 60 mg/d of raloxifene, or a placebo. The primary objective was the appearance of non-vertebral fractures, and changes in BMD and in the makers for bone turnover. With respect to the placebo group, the RR for vertebral fracture for the group treated with bazedoxifene at a dose of 20 mg/d was 0.58 (0.38-0.89); for the group treated with bazedoxifene at a dose of 40 mg/d it was 0.63 (0.42-0.96); and for the group treated with raloxifene, 0.58 (0.35-0.89). None of the three treatments reduced non-vertebral fractures in relation to the placebo, but in a post hoc analysis, bazedoxifene at a dose of 20 mg/d showed an RR in this type of fracture of 0.50 (0.28-0.90) in women with I) BMD in the femoral neck of ≤ 3T, or II) with one or more moderate or serious vertebral fractures, or III) with multiple light fractures.

8. Denosumab

As in the case of zoledronate and PTH 1-84, denosumab was already mentioned in the second version of these guides, but was not considered in the final assessment because the results of its pivotal study had not yet been published nor had it been approved for the market. Its efficacy has been evaluated in the FREEDOM (Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months) study, whose results have been published recently[16], although the drug is still not yet commercially available. The study consists of a randomised, double blind, placebo controlled clinical trial which involved 7868 women between 60 and 90 years of age with values of BMD of less than -2.5 T in the lumbar spinal column or whole hip. For ethical reasons women who presented with BMD lower than -4.5 T in the aforementioned areas, and those who had previously suffered from one serious, or two moderate fractures, were excluded. The patients were assigned 60 mg. of denosumab, or the placebo, subcutaneously every 6 months for 3 years. The principal objective of the study was the appearance of new vertebral fractures, while the secondary objectives included the appearance of non-vertebral or hip fractures. The study of the following adverse effects was established beforehand: infections, neoplasic processes, hypocalcemia, delay in healing of fractures and osteonecrosis in the jaw bone. The number of women included in the analysis of vertebral fractures was 7393. The RR for new radiographic vertebral fracture was 0.32 (0.26-0.41). The RR for non-vertebral fracture was 0.80 (0.67-0.95) and for the hip, 0.60 (0.37-0.97). The reduction in symptomatic vertebral fractures was similar to that for the radiographic fractures. Not a single example of any of the adverse reactions to denosumab listed above, was observed. Although a higher incidence of eczema (3% vs 1.7%), flatulence (2.2% vs 1.4%) and serious celulitis (0.3% vs one patient [<0.1%]), was noted.

The level of evidence is 1b, with a grade of recommendation of A for the reduction of vertebral and non-vertebral, and hip, fractures.

9. Flouride

Numerous clinical trials have been carried out with fluoride, with disparate results. In 2008 a meta-analysis was published[17] whose conclusion is that fluoride is efficacious in reducing osteoporotic fractures when administered in specific doses. It included 25 studies, and its overall results show an absence of the effect of fluoride on both vertebral and non-vertebral fractures. However, with a daily dose ≤ 20 mg of fluoride (152 mg of monofluorophosphate or 44 mg of sodium fluoride) a significant reduction is observed in both vertebral fractures (OR = 0.3; 0.1-0.9) and non-vertebral fractures (OR = 0.5; 0.3-0.8).

These Guides do not make recommendations on the use of non-approved drugs even for their application as a treatment for osteoporosis.

Osteoporosis in men

We have not found a single work which presents new data on efficacy in the reduction in risk of fracture in male osteoporosis in relation to comments in the second version of the SEIOMM Guides. The refractory study of work on zoledronate[7] included males, but the corresponding results have not been commented on in an independent publication.

By analogy with aledronate and risedronate, and given that there are no reasons to think that the effect of zoledronate should be different in women from in men, SEIOMM includes zoledronate among those drugs recommended for treatment of male osteoporosis. Similar reasons meant that the second version of the Guides recommended the use of teriparatide for osteoporosis in males with high risk of fracture, a recommendation which has subsequently been endorsed by the EMEA.

Steroidal osteoporosis

With reference to osteoporosis related to glucocorticoids, for the production of this update we have included two works, one on teriparatide, and the other on zoledronate.

1. Teriparatide

The efficacy of teriparatide in glucocortisoidal osteoporosis has been studied in a randomised, double blind clinical trial with active control, in which were compared the effect of 20 μg of PTH 1-34/d. with 10 mg of aledronate administered daily over 18 months[19]. It involved 428 men and women from 22 to 89 years of age with osteoporosis who had received glucocorticoids at a dose equivalent to or higher than 5 mg daily of prednisona for at least 3 months. The primary objective consisted of the changes in BMD of the lumbar spinal column. The secondary objectives were changes in BMD for the whole hip, in the markers, in the incidence of fractures and security data. The percentage of patients who experienced a new vertebral fracture in the group assigned PTH 1-34 was 0.6%, and in those assigned aledronate, 6.1% ($p = 0.004$). There were no significant differences in non-vertebral fractures.

A prolongation to 3 years, whose results were presented at the Conference of the ASBMR in 2008, confirmed the significant difference regarding vertebral fractures (1.7% vs 7.7%; $p = 0.007$[20]). It continued without there being significant differences in non vertebral fractures.

The level of evidence in the trial is 1b, and supports the assertion that PTH 1-34 possesses a greater efficacy than aledronate in the reduction of vertebral fractures in patients treated with glucocorticoids (recommendation A).

2. Zoledronate

The efficacy of zoledronate in steroidal osteoporosis has been studied in a non-inferiority trial[21], lasting a year, which compared the effects of zoledronate, administered intravenously at a dose of 5 mg/year, with those of risedronate, administered orally at a dose of 5 mg/day. The population of this study was made up of 383 women who were being treated with 7.5 mg of prednisone. The intervention qualified as "treatment" when the women had been receiving the corticoid for more than three months, and as "prevention" when they had been receiving it for less time. The primary objective it considered were changes in BMD in the lumbar spinal column, and the limit of the margin of non-inferiority was set at -0.7% for the treatment, and at -1.12% for the prevention. The secondary objectives were changes in the apendicular BMD and the incidence of vertebral fractures. All the IC points of the differences for the treatment group (limits 0.67-2.05) and for the prevention group (limits 1.04-2.88) were within the non-inferiority margin. In fact, zoledronate causes increases in BMD significantly greater that zoledronate in the lumbar spinal column, as much in treatment (4.06 ± 0.28% vs 2.71 ± 0.28%; $p < 0.0001$) as in prevention (2.60 ± 0.45% vs 0.64 ± 0.46%; $p < 0.0001$). They were also higher in the femoral neck (1,45 ± 0,31% vs 0,39 ± 0,30%; 1,30 ± 0,45% vs -0·03 ± 0,46%; $p < 0,005$ in both cases). No differences in the incidence of fractures was observed.

The trial has a level of evidence of 1b, and allows a recommendation for the use of zoledronate in glucocorticoidal osteoporosis with a level of recommendation A.

Calcium and vitamin D

During the time which has passed since the editing of the second version of the Guides a diverse number of trials and meta-analyses in relation to the usefulness of both substance in the treatment of osteoporosis have been carried out. However, we do not consider it necessary to consider them in this update, since not one case results in a single change in the recommendations made in these Guides. In the case of these substances is it concluded that "Female patients treated with antiresorptive or anabolics should receive adequate calcium and vitamin D supplements" (recommendation A).

As in the majority of the trials considered in the second version, so in those included in this update calcium and vitamin D was administered both to those patients assigned to the treatment groups, as well as those assigned to the placebo group, which is one of the reasons for recommending its use in patients being treated for osteoporosis.

General conclusion

Since the editing of the current version of the SEIOMM Guides to osteoporosis, a range of works have appeared with information on the efficacy of different drugs in the reduction of the risk of osteoporotic fractures.

Independently of whether these works carry data of interest on the use of the different drugs to which they refer, the Committee charged with producing this update to the Guides considers that the contents of the information referred to only advises the introduction of one change in the algorithm proposed in the current Guides. This change refers to the inclusion of zoledronate.

Zoledronate shares with aledronate and risedronate –the drugs proposed as standard treatment– its efficacy over the three types of fracture: vertebral, non-vertebral, and hip. Its administration, is also very comfortable –once a year– which can facilitate adherence. However, it has some inconvenient aspects, such as its intravenous use and its somewhat higher cost. These reasons have caused us to include zoledronate in the algorithm within the group of standard treatments, although indicating the necessity of assessing with the patient which type of drug is preferable to them. Probably, considering all the aspects together, zoledronate constitutes the alternative, within those drugs of choice, for patients who want to avoid taking drugs orally, or who prefer not to be dependent on taking a drug every week (e.g. polymedicated patients). The committee is aware, however, that its intravenous administration can pose a limit to the use of this drug in those cases in which there is no adequate means available, as can occur in Primary Care Centres.

PTH 1-84 has not demonstrated its efficacy in non-vertebral fractures, and as a consequence the Committee charged with the production of this update found no reason to place it with teriparatide. Its therapeutic characteristics place it, on the contrary, together with the drugs which only reduce vertebral fractures.

Otherwise, although some drugs included in the current algorithm can be seen to have strengthened their position through data provided more recently, this Committee considers that the basic scheme of the aforementioned algorithm should be maintained in its current form, considering the drugs of choice to be aledronate and risedronate, to which is now added zoledronate for occasions when the patient or the doctor thinks that annual intravenous administration of the drug is preferable. In a case in which the doctor thinks that there is an inadequate therapeutic response, or in situations of high risk of fracture (equivalent to the presence of two previous fractures), it is recommended that teriparatide should start to be used, and should continue for 24 months after an antiresorptive (it should be noted that in the previous version it was recommended that the treatment should only last for 18 months, this having been changed by the EMEA). The algorithm indicates that when there are other reasons for not using the standard treatment (poor tolerance, personal preference, etc.), the use of other drugs can be considered, essentially strontium and ibandronate. Finally, in cases in which a female patient has a high risk of fracture of the lower hip (densitometry of the hip above the range for osteoporotics), especially if there is an added risk of breast cancer, one can have recourse to raloxifene.

The recommendation for male osteoporosis remains the same as that in the previous document (aledronate and risedronate as first choice, etidronate and calcitonin as alternatives, and teriparatide in cases of high risk of fracture or of inadequate response), to which is now added zoledronate as a consideration to take into account from the start when the patient or the doctor prefers it.

The scheme for steroidal osteoporosis is much the same: aledronate and risedronate as a first choice, zoledronate also as a first choice if it is considered preferable in the specific circumstances that pertain to the case, and teriparatide if the risk of fracture is high or the response is not thought adequate. The indications for zoledronate and teriparatide did not figure in the earlier document.

Finally, we would like to stress that the application of whichever algorithm should be carried out with flexibility, taking into account the preferences of the patient, the opinions of the doctor and the possibilities of the health system. These factors are especially important when it is necessary to take decisions in respect of drugs which are found at the same level of choice.

Representatives of other Spanish scientific societies who have evaluated the Guides and formulated opinions on them

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ANNEX 1
Committee of Experts of the SEIOMM

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