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. The bisphosphonates constitute the group of drugs most commonly used for the treatment of this disease and are the first choice according to the SEIOMM guides. Among the bisphosphonates, zoledronic acid is the most potent third generation nitrogenated bisphosphonate currently on the market. 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. Zoledronic acid has an affinity for bonding with hydroxyapatite higher than other bisphosphonates and is the most powerful inhibitor of farnesyl-diphosphate-synthase and of bone resorption.

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. In turn it produces an increase in bone mineral density and a reduction in markers for bone turnover. 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). 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, raloxifene, tibolone, hormonal therapy, tamoxifen, ipriflavone, medroxyprogesterone), whilst in the second group were classed patients who had taken permitted antisteoporotic drugs. This excluded patients who had taken, at any time, parathyroid hormone, sodium and strontium fluoride, anabo-
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%, 53% 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. 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). 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.

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. 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.

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).
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 study showed that zoledronic acid also improved some strength indices. After three years of treatment, the resistance to bone compression improved significantly ($p \leq 0.001$) in those patients who had taken zoledronic acid in relation to patients treated with a placebo. 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. 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 ($p= 0.003$).

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

<table>
<thead>
<tr>
<th>Type of fracture</th>
<th>Placebo</th>
<th>Zoledronic Acid</th>
<th>Relative risk (IC del 95%)</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphometric vertebral fracture (stratum I)</td>
<td>310 (10.9)</td>
<td>92 (3.3)</td>
<td>0.30 (0.24-0.38)</td>
<td>$p&lt; 0.001$</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>88 (2.5)</td>
<td>52 (1.4)</td>
<td>0.59 (0.42-0.83)</td>
<td>$p&lt; 0.002$</td>
</tr>
<tr>
<td>Non-vertebral fracture</td>
<td>388 (10.7)</td>
<td>292 (8.0)</td>
<td>0.75 (0.64-0.87)</td>
<td>$p&lt; 0.001$</td>
</tr>
<tr>
<td>Any clinical fracture</td>
<td>456 (12.8)</td>
<td>308 (8.4)</td>
<td>0.67 (0.58-0.77)</td>
<td>$p&lt; 0.001$</td>
</tr>
<tr>
<td>Clinical vertebral fracture</td>
<td>84 (2.6)</td>
<td>19 (0.5)</td>
<td>0.23 (0.14-0.37)</td>
<td>$p&lt; 0.001$</td>
</tr>
<tr>
<td>Multiple ($\geq 2$) morphometric vertebral fractures (stratum I)</td>
<td>66 (2.5)</td>
<td>7 (0.2)</td>
<td>0.11 (0.05-0.23)</td>
<td>$p&lt; 0.001$</td>
</tr>
</tbody>
</table>

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). 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 < 2.0 mmol/L or a life expectancy of less than six months. As in HORIZON-PFT, 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.8 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 known9. However, only one in five patients who have suffered a fracture will follow on with a treatment for osteoporosis10, and it is estimated that 20% of women who have suffered a vertebral fracture will present with another fracture within a year11. 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 alendronate taken orally weekly in postmenopausal patients with low BMD12. 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 year13.

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.14 evaluated in 302 men affected by osteoporosis the effect of 5 mg i.v. annually of zoledronic acid as against 70 mg weekly of alendronate. 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 continuous increase in concentrations over the following six months. On the other hand, histological studies 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 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 concerning23,24. Treatment with glucocorticoids is 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 glucocorticoids25. 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 sub-groups, 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 sub-group, 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-protection25.

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 trauma26. 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 antosteoporotic drugs are prescribed abandon the treatment and, after 12 months, the majority take less than 80% of the pills prescribed27-30. This poor adherence to oral biphosphonates compromises their efficacy in reducing fractures and increases medical costs31,32, above all in older disabled adults, who often cannot follow the administration regime properly and strictly33.

Weekly treatments provide a better adherence than daily treatments, but even so, a sufficient adherence is only reached in around 50% of patients27,30. 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 density39. 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 equal34. 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.

**Tolerability**

In general, if we compare the tolerability of patients to zoledronic acid as against a placebo, this has been good. 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 38.5% 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 myalgia and pyrexia were significantly higher in the group which received the zoledronic acid.

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.

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-PTF 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.

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. However, in the HORIZON-PTF 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. Four patients who received zoledronic acid developed osteonecrosis in the knee or hip, compared with three patients in the placebo group. 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.

Finally, a slight increase in the risk of adverse inflammatory ophthalmological events in the 15 days following the perfusion was confirmed, 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 bisphosphonate 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, steroideal 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.

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. 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. 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. 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>
<thead>
<tr>
<th>Active principal</th>
<th>Commercial name</th>
<th>Dose. Period. Method of administration</th>
<th>Presentation</th>
<th>Packet cost 28 days (Euros without VAT)</th>
<th>Annual cost (Euros without VAT)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zoledronic acid</td>
<td>Aclasta</td>
<td>5 mg. Annual i.v.</td>
<td>Bottle 100 ml</td>
<td>406.39</td>
<td>406.39**</td>
</tr>
<tr>
<td>Alendronate</td>
<td>Several generics</td>
<td>70 mg. Weekly. Oral</td>
<td>Tablets. Packages with 4</td>
<td>15.42</td>
<td>200.46</td>
</tr>
<tr>
<td>Alendronate + Vitamin D</td>
<td>Fosavance</td>
<td>70 mg. Weekly. Oral</td>
<td>Tablets. Packages with 4</td>
<td>27.47</td>
<td>357.11</td>
</tr>
<tr>
<td>Risedronate weekly</td>
<td>Generics</td>
<td>35 mg. Weekly. Oral</td>
<td>Tablets. Packages with 4</td>
<td>22.93</td>
<td>298.09</td>
</tr>
<tr>
<td>Risedronate monthly</td>
<td>Acrel. Actonel</td>
<td>75 mg. Monthly 2 day. Oral</td>
<td>Tablets. Packages with 2</td>
<td>33.32</td>
<td>399.84</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>Bonviva. Bondenza</td>
<td>150 mg. Monthly. Oral</td>
<td>Tablets. Packages with 1</td>
<td>33.32</td>
<td>399.84</td>
</tr>
<tr>
<td>Strontium ranelate</td>
<td>Protelos. Osseor</td>
<td>2 g. Daily. Oral</td>
<td>Envelopes. Packages with 28</td>
<td>47.49</td>
<td>617.37</td>
</tr>
<tr>
<td>PTH 1-34</td>
<td>Forsteo</td>
<td>20 μg. Daily. Sub-cutaneous</td>
<td>Preloaded pen. Packages with 28</td>
<td>384.79</td>
<td>5,002.87</td>
</tr>
<tr>
<td>PTH 1-84</td>
<td>Preotact</td>
<td>100 μg. Diaria. Sub-cutaneous</td>
<td>2 cartridges 14 dose c/u</td>
<td>380.95</td>
<td>4,952.35</td>
</tr>
<tr>
<td>Nasal calcitonin</td>
<td>Miacalcic. Several</td>
<td>200 UI. Daily. Nasal</td>
<td>Nebulizer Packages with 28</td>
<td>72.13</td>
<td>937.69</td>
</tr>
</tbody>
</table>

*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.
**Bibliography**


