Introduction
Strontium ranelate is a therapeutic agent introduced in recent years for the treatment of osteoporosis with dual action on bone metabolism. The conditions which need to be satisfied by any drug for its use in the treatment of osteoporosis include safety and efficacy in the prevention of fractures. The evidence in relation to strontium ranelate come principally from the two multi-centric, clinical reference trials in phase 3, the SOTI (Spinal Osteoporosis Therapeutic Intervention) study and the TROPOS (Treatment of Peripheral Osteoporosis) study. The first was designed to access the preventative effect on vertebral fractures, whilst the second had as an objective the evaluation of non-vertebral fractures. These are the anti-osteoporotic drug trials which give results over the longest term, 4 years for the first and 5 for the second. Additional data comes from other older trials in phase 2, the STRATOS (Strontium Ranelate for Treatment of Osteoporosis) trial and the PREVOS (Prevention of Osteoporosis) trial which had the objective of assessing the effect on bone mass and biochemical markers for bone turnover in patients with established vertebral fractures in the first, and in the second, in women in the first years of menopause.

Safety of strontium ranelate
The SOTI and TROPOS studies included 3,352 women who received treatment with strontium ranelate, of whom 2,315 followed the treatment for at least 36 months. The adverse effects detected in these patients were no different from those observed in the group treated with placebos, and in general, were moderate and transitory. The most frequent were related to the digestive system: nausea (6.6% and 4.3% respectively) and diarrhoea (6.5% and 4.6 % respectively). Both adverse effects diminished after the first 3 months of treatment. In terms of the biochemistry, a small reduction in the concentration of blood calcium and an increase in blood phosphate was observed, neither clinically significant. Table 1 includes the adverse effects most frequently detected in these two trials. In patients older than 80 years the most frequent adverse effect was headache, 3.3% in the group with ranelate as opposed to 1.7% in the control group with a confidence interval of 95%: 0.01-3.3 followed by the adverse effects of the digestive system.

One of the controversial problems is venous thrombosis. Although taken separately, in each of the studies no increase in thromboembolic disease was found, in a subsequent analysis of aggregated data, and increase was found. A meta-analysis of the two reference studies in phase 3 found that after 5 years of treatment with strontium ranelate the annual incidence of cases of thromboembolic disease was 0.9%, as opposed to 0.6% in the placebo group, with a relative risk (RR) or 1.4, CI 95%; 1.0-2.0. The cause of this effect is unknown and does not have a reasonable scientific explanation. As a consequence, the technical information for the product includes the recommendation that precautions should be taken with patients with increased risk of thromboembolic disease, especially in cases with previous history of venous thromboembolism. Recently, this effect has been investigated using the classic general medicine
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least 5 years. They were randomly selected into
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summary of these results, given that these data are

Results of using strontium ranelate
There is much data related to the treatment of
osteoporosis with strontium ranelate. That the
treatment is considered efficacious is due to its
capacity to reduce the frequency of osteoporotic
fractures. The known data are related to vertebral
and non-vertebral fractures. In addition, there are
data concerning surrogates of fractures, such as
BMD and histomorphometry. We will present a
summary of these results, given that these data are
commented on in greater detail in another chapter
of this monograph.

Prevention of vertebral fractures
The first great reference study, called, in its abbrevi-
vated form, SOTI, included 1,649 women over 50
years of age, whose average age was 69 years,
having been postmenopausal for a period of at
least 5 years. They were randomly selected into
two groups, one treated with 2 mg of strontium
ranelate and the other with a placebo. In addition
both groups received calcium and vitamin D sup-
plements to guarantee the provision of the recom-
manded daily dose. All the women had at least
one earlier vertebral fracture due to their fragility,
and a lumbar bone mineral density (BMD) below
0.840 g per cm² measured by a Hologic densito-
meter, equivalent to a T-score of -1.9. The assess-
ment of the vertebral fractures was made through
Genant’s quantitative morphometric method in lat-
eral X-rays of the lumbar and thoracic spinal col-
um, taken at their inclusion in the trial and annu-
ally during the follow up.

A decrease in the frequency of radiographical
vertebral fractures was observed of 49% (6.4% as
opposed to 12.2% RR 0.51; CI 95%: 0.36-0.74) in
the group treated with strontium ranelate at the
end of the first year of follow up. In the same peri-
od, the risk of symptomatic vertebral fractures was
reduced by 52% (3.1% as opposed to 6.4%; RR=
0.48; CI 95%: 0.29-0.80). At the end of the three
years of treatment the results were similar. The
radiological vertebral fractures were reduced by
41% (20.9% as opposed to 32.8%; RR= 0.59; CI
95%: 0.48-0.73) and the symptomatic fractures by
38% (11.3% as opposed to 17.4%; RR= 0.62; CI
95%: 0.47-0.83). At the end of the fourth year the
reduction in risk of radiological fracture was 33%
(RR= 0.67; CI 95%: 0.55-0.81; p<0.001). The TROPOS study was designed to assess the
efficacy of strontium ranelate in the prevention of
non-vertebral fractures, but results were also
obtained for vertebral fractures. In 71% of the 5091
women included in this study, x-rays of the spinal
column were taken and it was observed that
66.4% of them had earlier fractures, which was a
criterion for inclusion in the SOTI study. After 3
years of treatment, a reduction in risk of vertebral
fractures of 39% (RR= 0.61; CI 95%: 0.51-0.73) was
observed in those women who had been incorpo-
rated in the group having treatment with strontium
ranelate, there already having been observed after
the first year, a reduction of 45% in the risk of frac-
ture (RR= 0.55; CI 95%:0.39-0.77; p<0.001). This
reduction affected both those women with an ear-
lier vertebral fracture and those who did not have
previous fractures.

A joint analysis was carried out of the results
of the third year of both the SOTI and TROPOS stud-
ies. 5082 women were evaluated, in whom the
risk of vertebral fracture was reduced to 40% (RR=
0.60; CI 95%: 0.65-0.87). The anti-fractural result
observed during the first three years was main-
tained during the extension phase up to the fifth
year. In these two last years, a tendency to a
reduction in efficacy was observed. However, this
fact was not interpreted as a reduction in the anti-
fractural effect of the drug, but to the fact of the
patients remaining in the study brings with it a
loss of randomness in distribution, since those
patients remaining in the placebo group are those
who have a lower risk of fracture.

One of the characteristics of the population
included in the SOTI and TROPOS studies is the
large group of women over 80 years of age who
made up over 20% of the total. In a sub-analysis
of the results of this group a reduction in risk of fracture of 32% was observed. But the anti-fractur- al effect is not very different in the remaining age groups, since in the youngest (less than 70 years of age) the reduction was 37%, and 42% in those women between the ages of 70 and 80. The number of patients it is necessary to treat (NTN) to avoid a vertebral fracture at three years is 13.

With the objective of seeing if the effect was independent of the risk of fracture in the patients, a sub-analysis was carried out, analysing the efficacy according to the number of earlier vertebral fractures. The main risk to these women was verified in the placebo group, since the incidence of new vertebral fractures increased according to the number of previous fractures, being 40.3% higher in the group with two or more fractures. In the group of patients treated there was a reduction in the risk of new fractures independent of the number of fractures they had before the start of treatment. 25.2% in patients with only one fracture and 40.3% in those who had two or more fractures. The risk of experiencing a first fracture, a second, or more than two fractures was reduced by 48%, 45% and 33% respectively.

The drug was also efficacious in women with osteopenia, both in those who had a previous fracture, of 41% (RR 0.59; CI 95%: 0.43-0.82), as well as those who did not, of 38% (RR 0.62; CI 95%: 0.44-0.88).

Prevention of non-vertebral fracture
The efficacy of treatment with strontium ranelate in the prevention of non-vertebral fractures was investigated in the TROPOS trial, which included, as we have already stated, 5091 women with an average age of 77 years. The criteria for inclusion were to have a BMD in the femoral neck lower than 0.600 g/cm², which is the equivalent to a T-score of -2.2, and to be older than 74 years or maternal history of fracture. The patients were randomly chosen to receive 2 g of strontium ranelate or placebo, and received calcium and vitamin D supplements.

All non-vertebral fractures were recorded, with the exception of those not related to osteoporosis: coccyx, cranium, jaw, face, phalangeal and ankle. In the 3 year follow up period, there was a reduction of 16% in all non-vertebral fractures (11.2% as opposed to 12.9%; RR= 0.84; IC 95%: 0.702-0.995; NTN to avoid one fracture was 49). The principal non-vertebral fractures considered were of the hip, wrist, pelvis, sacrum, ribs, sternum, clavicle and humerus. There was a reduction of 19% (8.7% as opposed to 10.4%; RR= 0.81; IC 95%: 0.60-0.98; NTN= 59). The global risk of fracture of the hip was reduced by 15%, but the difference was not significant since the study was not designed with sufficient power to investigate this anti-fractural effect. However, in a sub-group of high risk patients, aged over 74 years and BMD with a T-score lower than -2.3, there was a reduction of 36% in hip fractures (4.3% as opposed to 6.4%; RR= 0.64; IC 95%:0.412-0.997; NTN= 48).

In the period of extension to 5 years, the TRO- POS study the efficacy was maintained, with a reduction of 15% in the reduction of non-vertebral fractures (RR= 0.85; IC 95%: 0.73-0.99). The SOTI study was not powerful enough to assess the efficacy in relation to non-vertebral fractures. However, the fractures in 234 women after 3 years were recorded (with an incidence of 15.5% as opposed to 16.8%; RR= 0.90; IC95%: 0.69-1.17). In the study of the aggregated data from the two studies – SOTI and TROPOS – the global reduction in non-vertebral fractures was 15% (11.6% as opposed to 13.1%; RR= 0.85; IC 95%: 0.74-0.99). In the SOTI and TROPOS cohort of over 80 years, the reduction in the risk of non-vertebral fracture was 1% (14.2% as opposed to 19.7%; RR= 0.69; IC 95%: 0.52-0.92).

As with other chronic diseases, the effect of treatment is related to compliance. In those patient with good compliance with the treatment the risk of fracture reduces to 38% in relation to those patients who are non-compliant. Compliance in those patients in the TROPOS study was very high at the end of 5 years of follow up, higher than 80%.

Bone mineral density and makers for bone remodelling
Treatment with strontium ranelate increases BMD considerably. After 3 years of treatment the SOTI study noted an increase of 14.8% in the lumbar spinal column and 9.8% in total hip with respect to that observed in the placebo group. The period of extension of the TROPOS study showed an increased BMD in the lumbar spinal column of 4.9%, 1.8% in the femoral neck, and 2% in the total hip.

However, this major increase in BMD measured by double energy X-ray absorptiometry

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**Table 1. Adverse effects described in the clinical trials SOTI and TROPOS**

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Strontium ranelate (%)</th>
<th>Placebo (%)</th>
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<tbody>
<tr>
<td>Nausea</td>
<td>6.6</td>
<td>4.3</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>6.5</td>
<td>4.6</td>
</tr>
<tr>
<td>Loose faeces</td>
<td>1.1</td>
<td>0.2</td>
</tr>
<tr>
<td>Headache</td>
<td>3.0</td>
<td>2.4</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>2.1</td>
<td>1.6</td>
</tr>
<tr>
<td>Eczema</td>
<td>1.5</td>
<td>1.2</td>
</tr>
<tr>
<td>Allergic dermatitis</td>
<td>1.0</td>
<td>0.5</td>
</tr>
</tbody>
</table>
(DXA) requires an interpretation due to the physical characteristics of strontium. Its high atomic number attenuates the X-rays more than calcium, which produces an overestimation of the values of BMD. Blake has studied this phenomenon quantitatively and calculates that the artificial component of the density could approximate to 50%.

The SOTI study studied the modifications produced in the markers for bone formation and resorption. These biochemical markers are an indirect measure of bone metabolism. They are useful as indicators of the therapeutic response and are an indirect measure of compliance. The SOTI study observed that the bone iso-enzyme alkaline phosphatase increased by 8.1% more in patients treated than in those in the placebo group from the first three months of treatment. In the case of the markers for resorption, the C-terminal with bridges fragment (CTX) diminished 12.2% in the first few months. This behaviour is different from the increase which the anabolics produce and the significant decrease produced by the most commonly used anti-resorptives. The results observed in the STRATOS and PREVOS studies had a similar profile. These modifications are compatible with the action mechanism proposed or strontium ranelate which is that it stimulates the formation and reduces the resorption of bone.

Histology

There are biopsy data from the iliac crest which come from the STRATOS, SOTI and TROPOS studies, obtained over 5 years of treatment. The positive effect on bone formation is confirmed by the finding of an increase in the osteoblastic surface area and in the rate of mineral apposition in the trabecular and cortical bone. No changes were seen in the frequency of activation. The effect on the parameters of bone resorption indicates its reduction, although not statistically significant. Neither were any changes in primary bone mineralisation found. Recently, the results of a 3D using micro-μTAC study were published, observing that treatment with strontium ranelate improves the indices which contribute to an increase in the biomechanical competence of bone and which explain the anti-fractural effect of strontium.

Conclusions

The available evidence indicates that strontium ranelate is a safe drug, with a preventative effect on vertebral and non-vertebral fractures. This effect is maintained for at least 5 years and is independent of age, including in women over 80 years of age. Prevention is seen in women with osteopenia, with non-established osteoporosis and with fractures. The biochemical markers for bone turnover and data from biopsies confirm for us its dual action mechanism, moderately stimulating bone formation and inhibiting resorption.

Bibliography