Other studies with strontium ranelate: Analysis of efficacy

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Introduction
The efficacy of strontium ranelate (SR) in the reduction of fractures having already been described in another chapter of this monograph, we are going to analyse other important aspects of the studies which support the assessment of its efficacy. These aspects are:
1. Quality of life in the short and long term in treatment with SR.
2. Efficacy of SR in patients over 80 years of age.
3. The relationship of the baseline state of bone turnover to anti-fractural efficacy.
4. Baseline risk factors and anti-fractural efficacy of ST.

Quality of life in the short and long term in treatment with SR
Osteoporosis is characterised by a decrease in bone mass and a deterioration in the microarchitecture of bone tissue, which explains the weakness of the bone and the consequent risk of fractures.
Epidemiological studies have confirmed that postmenopausal osteoporosis is a very extensive and prevalent disease. The morbidity of osteoporosis is due, above all, to fractures of the hip, vertebrae and distal radial extremities. Hip fractures produce acute pain and loss of function and almost always result in hospital admission. Recuperation rates are low and rehabilitation is often incomplete. Many patients end up staying in a centre for the chronic sick. Vertebral fractures can produce acute pain and loss of function but are also associated with serious symptoms. Vertebral fractures often recur, and the consequent incapacity increases with their number. Fractures of the distal radial extremities also produce acute pain and loss of function but recuperation is usually satisfactory.
In addition to the pain and functional changes, the fractures can reduce mobility and social relations and result in emotional problems. All these characteristics shape the quality of life.
Quality of life covers all aspects of life, including health, the environment, economic matters and human rights. Health-related quality of life (HRQL) is a subgroup of quality of life which affects physical, emotional and social well-being.
Clinical trials concerning osteoporosis carried out to date, have been based on variables measured with imaging techniques. However, these measurements do not adequately reflect the degree to which the daily activities of the patient come to be affected and, as a result, are not appropriate for the evaluation of their incapacity and its symptoms. The quality of life has, in recent years, become an important variable in clinical trials. To assess the repercussions of a fracture due to osteoporosis on the quality of life and the effects of different treatments for osteoporosis specific questionnaires which relate quality of life to health (HRQL) have been used as the main criteria for the assessment of clinical trials for osteoporosis.
Quality of life questionnaires have been classified as generic, specific to a disease, or specific to a study. Generic questionnaires contain general questions on state of health and can be used for different diseases. Some generic questionnaires
regarding HRQL, such as SIP (Sickness Impact Profile), SF-36 or NHP (Nottingham Health Profile), have been used with more frequently to understand the effect of osteoporosis on HRQL. These questionnaires can be applied to any population or disease, which allows a comparison to be made between those suffering different diseases. However, they show serious limitations because they do not explore in detail specific aspects of osteoporosis. For example, in some studies it has been confirmed that certain aspects, such as fear of falling and its consequent fracture, the ability to dress oneself without help, the impossibility of correctly carrying out housework, and desperation before an uncertain future, causes these patients suffering.

These matters are not included in generic questionnaires and their omission could result in an incomplete evaluation or bias in the HRQL of patients with osteoporosis.

There are also questionnaires specific to osteoporosis, such as OPTQoL (Osteoporosis Targeted Quality of Life)6, OPAQ (Osteoporosis Assessment Questionnaire)10, QUALEFFO (Quality of life questionnaire of the European Foundation for Osteoporosis)11, OQLQ (Osteoporosis Quality of Life Questionnaire)12 and OFDQ (Osteoporosis Functional Disability Questionnaire)13. The Quality of Life questionnaire in Osteoporosis (QUALIOST)14 has been developed as a metric for quality of life specifically for osteoporosis used in conjunction with one of those most widely-used as a generic tool – SF-36. QUALIOST is a questionnaire valid for 23 items which are expressed as a global assessment, and two sub-assessments (physical and emotional).

QUALIOST® and strontium ranelate (SR)
SR is a new anti-osteoporotic preparation studied in two broad phase 3 programmes called the SOTI (Spinal Osteoporosis Therapeutic Intervention) study15 and the TROPOS (Treatment of Peripheral Osteoporosis) study16. In the SOTI study, an international clinical trial, double blind and placebo controlled, 1,649 postmenopausal women with osteoporosis were examined; SR reduced the risk of vertebral fracture. This efficacy in relation to fractures results in clinical benefits, for example a 20% decrease in the rate of reduction in height and a 29% increase in the number of patients without back pain. Quality of life constitutes a secondary variable, assessed through two questionnaires: SF-36 and QUALIOST® at baseline and every 6 months. The main analysis is carried out after a 3 year follow up17-19. The change in the general scores revealed an improvement in the HRQL in the group treated with SR and a deterioration in the placebo group (p= 0.03). This improvement in quality of life of the SR group was confirmed by the change in the emotional and physical scores in this group, in comparison with the placebo group (p= 0.04 and p= 0.05 respectively), indicating beneficial effects on emotional and physical functions. The majority of the patients with SR (+31%) were without lumbar pain after three years of the study, compared with the placebo group (p= 0.005). The rates of therapeutic completion surpassed 80% in the phase III studies, which reflects the profile of tolerance, safety, and ease of administration of this medication20. There are more long term (4 years) data from the SOTI study in which 1,250 patients (87% of the intention to treat population) were followed21. Both SF-36 and QUALIOST questionnaires were analysed. In relation to the SF-36 questionnaire, significant differences were found between baseline values and those after treatment both in the individual dimensions of SF-36 (p= 0.043) and the General Perception of Health dimension (p= 0.012). The global score of QUALIOST was lower (indicating a better quality of life) in the group treated with SR than in the placebo group, and the differences between the baseline and final values were -0.06 in the SR group and 1.92 in the placebo group (p= 0.02). When the emotional and physical dimensions of QUALIOST are considered separately, a statistically significant difference between the baseline changes and those post-treatment is found in the group treated with SR with respect to the placebo group, both in the emotional (p= 0.012), and in the physical variable (p= 0.034).

The proportion of patients free from lumbar pain after four years of treatment was 28% higher in the group treated with SR than in the placebo group, with the differences between the baseline and final values were -0.06 in the SR group and 1.92 in the placebo group (p= 0.005). In fact 14.6% of the patients who received SR, vs 11.2% of those who received the placebo, were without lumbar pain after 4 years (RR= 1.28; 95% CI [1.08, 1.52]).

**Efficacy of strontium ranelate in older people**
Around 25-30% of the population which suffers fractures due to fragility in the community occurs in women over 80 years of age, due to the fact that this population has a high risk of all types of fracture, particularly non-vertebral fractures. In spite of this, there is little evidence that the existing therapies for osteoporosis reduce the risk either of vertebral or non-vertebral fractures in this age group.

A study has been carried out based on a pre-planned analysis of the results of two international studies, phase III, randomised, controlled by placebo, double blind – the SOTI (Spinal Osteoporosis Therapeutic Intervention) study15, and the TROPOS (Treatment Of Peripheral Osteoporosis) study16 which included 1,488 women, aged between 80 and 100 years, followed for three years21. An annual X-ray of the spinal column was carried out in 895 patients Only non-vertebral fractures confirmed radiologically were included. The results of this study showed that at baseline, there were no differences between the group which received the placebo and that which received treatment. In the intention to treat analysis, the risk of vertebral, non-vertebral and clinically symptomatic fractures (vertebral and non-vertebral) was reduced in one year by 59% (p= 0.002), 41% (p= 0.027), and 37% (p= 0.012), respectively. At the end of the third
year, the risk of vertebral, non-vertebral and clinical fractures was reduced by 32% (p= 0.013), 31% (p= 0.011) and 22% (p= 0.040), respectively. The medication was well tolerated and its safety profile was similar to that of young patients. What this shows is that, even in very old people, it is never too late to reduce the risk of fracture.

Relation of the baseline state of bone turnover with anti-fractural efficacy

The intensity of bone turnover is variable among women at risk of osteoporotic fractures. Strontium ranelate is an anti-osteoporotic treatment which increases bone formation and reduces bone resorption. It has been hypothesised that the already demonstrated anti-fractural efficacy of SR could be independent of the baseline levels of bone turnover. To check this hypothesis, the mixed data from the two randomised, double blind trials, SOTI and TROPOS, carried out with SR in women with osteoporosis, have been analysed. The patients were stratified in terciles, in accordance with baseline values of the biochemical markers for bone remodelling: bone alkaline phosphatase (b-ALP, as marker for bone formation, n= 4,995), and blood C-terminal telopeptide (sCTX, as marker for bone resorption, n= 4,891). After three years of treatment with 2 g/day of SR, or placebo, the risk of vertebral fracture and the bone mineral density (BMD) in the lumbar region were assessed.

In the placebo group, the relative risk of vertebral fracture increased in relation to the level of the tercile of the markers, it being 32% and 24% for the patients in the higher tercile for b-ALP and CTX respectively. In the SR group, the incidence of vertebral fracture was not significantly different between the different terciles. A significant reduction in vertebral fractures was observed in the three terciles of both markers, with a reduction of relative risk of fracture of 31% to 47% in relation to the placebo group. The reduction of risk did not differ between the different terciles (p= 0.513 for b-ALP, p= 0.290 for sCTX).

We can conclude that the efficacy of SR in reducing vertebral fractures is independent of the baseline values of the markers for bone turnover, supporting the idea that SR offers clinical benefits to osteoporotic women, independent of their metabolic state.

Baseline risk factors and the anti-fractural efficacy of ST

At present there are diverse treatments which have demonstrated their efficacy in the treatment of OP. It is possible that the therapeutic response to these treatments depends on the initial BMD or age of the patients, or that it could be dependent on other factors. SR has demonstrated, in two extensive international studies in postmenopausal women (SOTI and TROPOS), its efficacy in the reduction of vertebral and non-vertebral fractures.

An earlier analysis has grouped the data of these two studies (SOTI and TROPOS) (5082 patients, 2,536 treated with SR and 2,546 receiving the placebo), with an average age of 74 years and followed up over 3 years, and in which the influence of different baseline risk factors (age, baseline BMD, prevalent fractures, family history of OP, body mass index (BMI), and tobacco habit) in the efficacy of the treatment were analysed. The intention to treat principle was used, as well as the Cox model in the comparisons and the calculations of relative risk.

We know that SR reduces the risk of vertebral fractures (relative risk (RR = 0.60 [0.53-0.69]). The reduction in risk of vertebral fracture was 37% (p= 0.003) in women aged less than 70 years, 42% in women of between 70 and 80 years and 32% (p= 0.013 in those of at least 80 year of age, without any difference in the three groups. The RR of vertebral fractures was 0.28 (0.07-0.99) in the women with osteopenia, and 0.61 (0.53-0.70) in the case of osteoporosis and the baseline BMD was not a determinant of efficacy. The incidence of vertebral fractures increased in the placebo group in relation to the number of previous fractures, but this was not a determinant of the efficacy of SR. In 2,605 patients, the risk of presenting a first vertebral fracture was reduced in 48% (p<0.001). The risk of suffering a second vertebral fracture decreased in 45% (p<0.001; 1,100 patients). Also, the risk of presenting more than two vertebral fractures was reduced in 33% (p<0.001; 1,365). Family antecedence of OP, baseline BMI, and smoking were not determinants of the efficacy of SR, from which we can conclude that the efficacy of SR in reducing vertebral fractures in postmenopausal women is independent of baseline risk factors for OP.

Conclusions

Patients treated with SR have a reduced number of vertebral and non-vertebral fractures and this effect is independent of age, continuing in women of over 80 years of age, independent of BMD previous to the treatment, and independent of baseline risk factors. In addition, it has been shown that, in treated patients, SR improves the quality of life in an objective way.

Bibliography


