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STRONTIUM RANELATE: THE FIRST DUAL ACTION BONE AGENT

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SUMMARY

This edition of Medifile reviews a new drug, strontium ranelate. Protos® (strontium ranelate) is the first dual action bone agent registered for the treatment of postmenopausal osteoporosis to reduce the risk of vertebral and peripheral fractures, including the hip.

INTRODUCTION

Osteoporosis is defined as a systemic skeletal disorder characterised by decreased bone mass (measured as bone mineral density (BMD)) and micro-architectural deterioration of bone tissue, resulting in bone fragility and susceptibility to fracture, typically involving the spine, hip or wrist.[1] Bone formation and bone resorption are closely coupled in normal bone. However, the net rate of bone resorption exceeds the rate of bone formation in osteoporosis. This results in a decrease in bone mass without a defect in bone mineralization.[2]

Osteoblasts are cells that form the organic matrix of bone and then mineralise bone and *osteoclasts* are cells that break down bone. Osteoclast activity is increased in postmenopausal women because of decreased oestrogen and in men with prematurely decreased testosterone. Osteoblast activity decreases in women and men greater than 60 years old.[2]
Until recently pharmacological agents specific for the treatment of osteoporosis have been either *inhibitors of bone resorption* (e.g. bisphosphonates, hormone replacement therapy, selective oestrogen receptor modulators, calcitonin) or *promoters of bone formation* (e.g. parathyroid hormone).[1,3] However, in April 2006 Servier Laboratories launched Protos® (strontium ranelate 2mg), which is unique in that it increases bone formation and decreases bone resorption.[4] It is an orally active agent comprised of two atoms of stable strontium and an organic moiety (ranelic acid).[4,5] The dual action of strontium ranelate on bone metabolism dissociates bone formation and bone resorption by allowing continued bone production whilst decreasing bone resorption.[6] This action rebalances bone turnover in favour of the formation of new healthy strong bone.[7]

MODE OF ACTION

Strontium ranelate exerts its dual effect by:

- Stimulating the replication of osteoblast precursors and collagen synthesis thereby promoting bone formation[7]
- Decreasing osteoclast differentiation and their resorbing activity thereby reducing bone resorption[7]

EFFICACY

The efficacy of strontium ranelate for postmenopausal osteoporosis is based on 36-month data from two extensive Phase III clinical trials.

Table 1: Summary of TROPOS and SOTI Study Design[4,5,6]

	SOTI	TROPOS
Number of Patients	1649 osteoporotic postmenopausal women	5091 osteoporotic postmenopausal women
Mean Age	Mean age of 70 years	Mean age of 77 years
Entry Criteria	• At least one spinal fracture • Lumbar BMD ≤0.840g/cm^2 • Postmenopausal ≥5 years • At least 50 years old	• Femoral neck BMD ≤-2.5 SD • Postmenopausal • ≥74 years or between 70 and 74 years with one additional risk factor eg. previous post-menopausal osteoporotic fracture, frequent falls
Exclusion Criteria	• Severe conditions/diseases interfering with bone metabolism • Fluoride salts and bisphosphonates taken ≥14 days in previous 12 months • Oestrogen or calcitonin or calcitrol taken for ≥1 month in previous 6 months	• Diseases interfering with bone metabolism • Bisphosphonates taken for ≥14 days in previous year • Oestrogen, calcitonin, uoride salts, calcitrol, or 1-α-vitamin D taken ≥1 month during previous 6 months
Primary End Point	Incidence over time of new vertebral fractures	Incidence over time of all non-vertebral fractures (fractures of coccyx, skull, jaw, face, phalanx & ankle excluded as not regarded as being related to osteoporosis)
Secondary End Point	• BMD at lumbar spine • Markers of bone turnover • Non-vertebral fractures • Height loss	Major non-vertebral osteoporotic fractures (hip, wrist, pelvis, sacrum, ribs-sternum, clavicle, humerus)
Duration of Study	3 years	5 years but main statistical analysis at 3 years

Legend to Table 1: Bone mineral density (BMD), Standard Deviation (SD)

The **S**pinal **O**steoporosis **T**herapeutic **I**ntervention **(SOTI)** Trial included 1649 postmenopausal women with established vertebral osteoporosis and examined the effect of strontium ranelate on reducing vertebral fractures.[4] The **TR**eatment **O**f **P**eripheral **OS**teoporosis **(TROPOS)** Trial, conducted on 5091 postmenopausal women, evaluated the effect of strontium ranelate on peripheral (non-vertebral) fractures.[6] Both trials were double-blind, randomised and placebo-controlled studies with two groups ie: strontium ranelate 2g per day group versus the placebo group. Before inclusion into either trial, calcium and vitamin D were administered to normalise levels. This supplementation was continued during both studies.[4,5,6] Refer to Table 1 for a summary of the study design of both trials.

RESULTS OF SOTI**

The incidence of new vertebral fractures occurred in fewer patients in the strontium ranelate group than the placebo group. After the first year of treatment, patients taking strontium ranelate 2g per day had a 49 percent (p<0.001) lower risk of a new vertebral fracture versus placebo and a 52 percent (p=0.003) lower risk of symptomatic fracture. Over the entire study period of 3 years, there was a *41 percent (p<0.001) lower risk of a new vertebral fracture in the strontium ranelate group* as compared to the placebo group.[4]

The baseline bone mineral density (BMD) in the two groups was similar. At 3 years, differences between the placebo and treatment groups were 14.4 percent at the lumbar spine, 8.3 percent at the femoral neck and 9.8 percent at the total hip.[4]

The serum levels of bone-specific alkaline phosphatase *(a marker of bone formation)* **increased** by 8.1 percent (p<0.001) in the strontium ranelate group as compared to the placebo group at the third month of treatment and remained high during the three year study. Concurrently, the serum concentration of C-telopeptide cross-links *(a marker of bone resorption)* **decreased** by 12.2 percent at month 3 (p<0.001) in the strontium ranelate group compared to the placebo group and remained lower than placebo throughout the study.[4] Refer to Table 2 for a summary of the SOTI Trial results.

RESULTS OF TROPOS**

Non-vertebral fractures

Over a 3 year follow up period, there was a 16 percent (p=0.04) relative risk reduction in *all* non-vertebral fractures in the strontium ranelate group compared to placebo. The strontium ranelate group showed a 19 percent (p=0.031) risk reduction of *major* non-vertebral osteoporotic fractures (hip, wrist, pelvis, sacrum, ribs-sternum, clavicle, humerus).[6]

There was also a 15 percent reduction in the relative risk of experiencing a hip fracture. However, this figure did not reach statistical significance as the study was neither designed nor powered to demonstrate an anti-fracture efficacy at each individual site (i.e. hip level). In a subgroup of patients with high risk fractures (women ≥ 74 years and with a femoral neck BMD T-score ≤-3), there was a 36 percent reduction in the risk of hip fracture.[6]

Vertebral fractures

Vertebral fracture results could only be assessed in 3640 patients who had baseline & annual follow-up vertebral x-rays taken. In this sub-group there was a 39 percent (p<0.001) relative risk reduction of new vertebral fractures in the strontium ranelate group compared to placebo over a 3 year period.

66.4% (2416) of the patients in the sub-group had no prevalent vertebral fracture at baseline – in these patients the risk of occurrence of a first vertebral fracture was 7.7 percent in the strontium ranelate group and 14 percent in the placebo group over 3 years.[6]

In the sub-group of 1224 patients with at least one prevalent fracture at baseline (strontium ranelate

Table 2: Summary of Results of the SOTI Trial[4]

	Strontium Ranelate Group	Placebo Group	P-Value
% of patients with one new vertebral fracture over 3 years	17.7%	28.4%	P<0.001
% of patients with more than one new vertebral fracture over 3 years	6.4%	9.8%	P=0.02
Symptomatic vertebral fractures	11.3%	17.4%	P<0.001
Height loss of at least 1cm	30.1%	37.5%	P=0.003
Back pain	17.7%	21.3%	P=0.07
Non-vertebral fractures over 3 years	6.8% (n=112)	7.4% (n=122)	
BMD at lumbar spine at 3 years (adjusted for strontium content)	Increase from baseline of 6.8%	Decrease from baseline of 1.3%	P<0.001

Legend to Table 2: Percent (%), Bone Mineral Density (BMD)

group=587, placebo group=637), there was a 32 percent ($p<0.001$) reduced risk of a new vertebral fracture. The incidence of vertebral fractures in this sub-group was 22.7 percent for the strontium ranelate group and 31.5 percent for the placebo group, over the 3 years.[6]

Bone Mineral Density

Differences in BMD between the placebo and treatment groups at 3 years were 9.8 percent for the total hip and 8.2 percent for the femoral neck ($p<0.001$).[6]

SAFETY AND TOLERABILITY

Treatment with strontium ranelate was well tolerated in both the **SOTI** and **TROPOS** trials. The rate of adverse events, withdrawals due to adverse events and rate of compliance were similar in the treatment and placebo groups.[4,6] Refer to Table 3 for a summary of the adverse events.

In both studies, serum calcium levels were found to be decreased and serum phosphorous increased in the strontium ranelate group, compared to placebo. A slight decline in serum parathyroid hormone was found in both groups. However, these changes were without clinical consequences.[4]

CURRENT OSTEOPOROSIS TREATMENT AND STRONTIUM RANELATE

Currently, there are no data on direct comparisons between strontium ranelate and other available osteoporosis treatment.[4] However, using results from studies done on other osteoporosis drugs a *similar risk reduction of vertebral fractures* has been shown with strontium ranelate:[4]

- ***Strontium ranelate*** (Protos®) - In the **SOTI** trial, the risk of new vertebral fractures was decreased by 49 percent in the first year and by 41 percent over a three year period, as compared to placebo.[4]
- ***Alendronate*** (Fosamax®) – In the Fracture Intervention Trial, the risk of new radiographic vertebral fractures was 47 percent lower in the alendronate group as compared to the placebo group.[8]
- ***Risedronate 5mg*** (Actonel®) – According to results published by the Vert Study Group, the risk of new vertebral fractures with risedronate 5mg was reduced by 49% over 3 years compared with placebo.[9]
- ***Raloxifene*** (Evista®) – Results from a trial published by Ettinger et al showed that the risk of vertebral fractures, detected clinically or by radiography, was decreased by 30 to 50 percent in patients treated with raloxifene 60mg or 120mg for 3 years as compared to placebo.[10]
- ***Parathyroid hormone (PTH 1-34)*** (Forteo®) – At doses of 20ug and 40ug of PTH 1-34, the risk of one or more new vertebral fractures was reduced by 65 and 69 percent respectively as compared to placebo after 21 months of treatment.[3]

The *increase in lumbar spine BMD* with strontium ranelate also compares favourably with other osteoporosis treatment. All comparisons are against placebo:

- ***Strontium ranelate*** (Protos®) – 8.1 percent increase in BMD at the lumbar spine at 3 years after adjustment for the strontium content of bone[4]
- ***Alendronate*** (Fosamax®) – 6.2 percent increase

Table 3: Summary of Adverse Events during SOTI and TROPOS Trials[4,6]

	Strontium Ranelate Group	Placebo
SOTI TRIAL		
Rate of compliance	83%	85%
***Diarrhoea (1st 3 months)**	6.1%	3.6%
Gastritis	3.6%	5.5%
High levels of serum creatinine kinase (twice upper limit of normal)	3.4%	1.8%
TROPOS TRIAL		
Incidence of adverse events	87.9%	88.9%
Serious adverse events	24.7%	24.4%
Withdrawals due to adverse events	24.2%	21.6%
***Nausea (1st 3 months)**	7.2%	4.4%
***Diarrhoea**	6.7%	5.0%
Headache	3.4%	2.4%
Dermatitis and eczema	5.5%	4.1%
Gastritis	2.3%	2.7%

* After 3 months there was no difference between the groups concerning diarrhoea and nausea.

***Please note that 4-year data for SOTI and 5-year data for TROPOS are now available. However, since they were not available at the time of writing this article they have not been included in this review.**

Table 4: Price comparison of some of the available Osteoporosis drugs

Ingredient	Product	Quantity	SEP (incl VAT)
Strontium Ranelate	Protos®	28	R316.92
Alendronate	Fosamax® 10mg	28	R281.18
	Fosamax® 70mg	4	R302.28
	Osteobon® 10mg	28	R127.68
	Osteobon® 70mg	4	R171.00
	Fosagen® 70mg	4	R170.97
Risedronate	Actonel® 5mg	28	R269.23
	Actonel® 35mg	4	R272.39
Raloxifene	Evista®	28	R327.86

Legend to Table 4: SEP = Single Exit Price. Prices as per MediKredit price file 21 June 2006

in the lumbar spine BMD[8]

- ***Risedronate*** (Actonel®) – 5.9 percent increase in spine BMD at 3 years[9]
- ***Raloxifene*** (Evista®) – 2.6 to 2.7 percent increase in spine BMD (60mg and 120mg respectively)[10]
- ***Parathyroid hormone (PTH 1-34)*** (Forteo®) – 9 percent increase in spine BMD at 21 months of treatment with 20ug PTH[3]

PLACE IN THERAPY

At the recommended dose of 2g per day, strontium ranelate is relatively more expensive than recommended doses of other osteoporosis agents. Refer to Table 4 for a summary of the price comparisons.

Current South African guidelines for the treatment of osteoporosis are being reviewed by the National Osteoporosis Foundation of South Africa (NOFSA) and will only be available later this year. The Italian guidelines for the diagnosis, prevention and treatment of osteoporosis (SINOSSI, 2005) recommend strontium ranelate at the same degree as alendronate and risedronate which would relate to first line treatment.[11] However, strontium ranelate is recommended as an *alternative treatment* option in the draft recommendations by the Appraisal Committee of the National Institute for Health and Clinical Excellence (NICE) under the following circumstances:[12]

- If bisphosphonates are contra-indicated
- If the patient cannot comply to the special administration instructions of bisphosphonates
- If the patient is intolerant to bisphosphonates
- If the patient has not had satisfactory response to bisphosphonates

Limitations of Strontium Ranelate

- Intake of strontium ranelate with food, milk or calcium products significantly reduces strontium bioavailability. Therefore, it should be taken at least two hours after taking such products. [7]
- Strontium ranelate is excreted in breast milk and should not be used by pregnant and breastfeeding women.[7]
- Not recommended in patients with renal impairment.[7]
- Should be used with caution in patients with high risk of venous thromboembolism.[7]

CONCLUSION

The primary aim of osteoporosis treatment is the prevention of fractures. Current anti-resorptive agents prevent bone destruction by decreasing the rate of bone remodelling. This is reflected by a decrease in the markers of bone formation and bone resorption as shown in studies done with the bisphosphonates and raloxifene.[4,13] However, the mechanism of action of strontium ranelate differs in that bone formation is increased based on serum concentrations of bone-specific alkaline phosphatase and bone resorption is decreased on the basis of serum concentrations of C-telopeptide cross-links, as compared to placebo.[4]

Although there are currently no direct comparative trials between strontium ranelate and other registered osteoporosis treatments, the effect of strontium ranelate, compares favourably with other available osteoporosis treatments. However, it would be of benefit for head-to-head studies to be done to enable direct comparisons of the efficacy and safety of the different drugs.

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