Correction of vitamin D insufficiency with combined strontium ranelate and vitamin D₃ in osteoporotic patients

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Abstract

Objective: This study aims to investigate the efficacy and safety of oral fixed-dose combination of strontium ranelate 2 g/vitamin D₃ 1000 IU daily vs strontium ranelate 2 g daily for correcting vitamin D insufficiency in osteoporosis.

Design: A 6-month international, randomized, double-blind, parallel-group, phase 3 study.

Methods: A total of 518 men and postmenopausal women aged ≥ 50 years with primary osteoporosis ($T\text{-score} \leq -2.5$ s.d.) and serum 25-hydroxyvitamin D (25(OH)D) > 22.5 nmol/l were included. Patients were allocated to strontium ranelate 2 g/vitamin D₃ 1000 IU daily ($n=413$) or strontium ranelate 2 g daily ($n=105$). The participants received calcium 1 g daily. The primary endpoint was serum 25(OH)D at last post-baseline evaluation during 3 months.

Results: Both groups were comparable at baseline. Mean baseline of 25(OH)D was 44.1 ± 14.6 nmol/l. After 3 months, the percentage of patients with 25(OH)D ≥ 50 nmol/l was higher with strontium ranelate/vitamin D₃ vs strontium ranelate (84 vs 44%, $P<0.001$; adjusted between-group odds ratio = 6.7; 95% CI, 4.2–10.9). The efficacy of the fixed-dose combination on 25(OH)D was maintained at 6 months (86 vs 40%, $P<0.001$). Mean 25(OH)D was 65.1 and 49.5 nmol/l, respectively, after 3 months and 66.9 and 45.4 nmol/l after 6 months. Physical performance improved in both groups. Falls were 17 and 20% in the strontium ranelate/vitamin D₃ and strontium ranelate groups respectively. Parathyroid hormone levels were inversely correlated with 25(OH)D. No clinically relevant differences in safety were observed.

Conclusions: This study confirms the efficacy and safety of fixed-dose combination of strontium ranelate 2 g/vitamin D₃ 1000 IU for correction of vitamin D insufficiency in osteoporotic patients.

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Introduction

Vitamin D insufficiency is highly prevalent in older osteoporotic patients, who are particularly vulnerable to the bone weakening due to vitamin D insufficiency (1, 2). It is also common in the general population (3). Lack of sunlight, poor diet, and inadequate dietary supplementation are causes of vitamin D insufficiency. The severity of vitamin D insufficiency is reflected by serum 25-hydroxyvitamin D (25(OH)D), a marker of

vitamin D status. In this study, we used a 25(OH)D threshold of 50 nmol/l (20 ng/ml) to define vitamin D insufficiency, in line with the recommendations of the Institute of Medicine (IOM) and the European Society of Clinical and Economical aspects of Osteoporosis and Osteoarthritis (ESCEO) (4). Above this level, bone health is ensured by normalization of bone turnover and parathyroid hormone (PTH) levels (4, 5, 6). To improve

bone health, patients with $25(\text{OH})\text{D} < 50 \text{ nmol/l}$ should receive vitamin D supplementation (2) to reduce mineralization defects, bone turnover, and PTH levels, and to help reduce rates of frailty, fracture, and all-cause mortality (7).

Current guidelines recommend the prevention of osteoporosis in the elderly via pharmacological and nonpharmacological measures, including vitamin D and calcium supplementation in addition to osteoporosis treatment (8, 9, 10). There is a general consensus that elderly patients at risk of fracture or with osteoporosis should receive 800–1000 IU of vitamin D daily (11). Regular administration of vitamin D has been shown to be more effective than less frequent vitamin D administration, both in terms of efficacy and safety (12, 13, 14). Vitamin D at daily doses of 800–1000 IU has also been shown to reduce the risk of falls and fractures in the elderly (15, 16), as well as to improve balance, muscle strength, and muscle function (17, 18). Above this daily dose range, the ability of vitamin D supplementation to influence fracture-predicting parameters, like fall and bone mineral density (BMD), may stabilize or decline (19, 20). Vitamin D_3 , the currently recommended form of vitamin D, has been shown to have better efficacy and a longer duration of action than vitamin D_2 (10, 21), although these findings are not unanimously accepted (22). The quantity of vitamin D in food supplements is often insufficient, resulting in patients not receiving an adequate daily intake and adherence to vitamin D supplements is poor (2, 23). For these reasons, fixed-dose combinations of osteoporosis treatments and vitamin D at the recommended daily dose could be a valuable option for increasing patients' compliance with long-term vitamin D therapy.

The efficacy of strontium ranelate in osteoporosis has been demonstrated in a wide range of osteoporotic patients (24, 25, 26). A fixed-dose combination of strontium ranelate 2 g with vitamin D_3 1000 IU has been proposed to be an effective and convenient way to treat osteoporosis, while simultaneously ensuring that patients receive a recommended daily dose of vitamin D. This study investigated the efficacy and safety of daily fixed-dose combination of strontium ranelate 2 g/vitamin D_3 1000 IU vs daily strontium ranelate 2 g for the correction of vitamin D insufficiency in osteoporosis.

Subjects and methods

Study design

This 6-month international, multicenter, randomized, double-blind, parallel-group phase 3 study included

patients with primary osteoporosis from 55 centers in 13 countries. The first patient visit took place on January 28, 2010, and recruitment finished on July 13, 2010. The last visit was on January 14, 2011. Ethics Committee approval was obtained in participating countries, and all patients gave written informed consent at selection. The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki of 1964 (revised in Seoul in 2008). The trial is registered on www.controlled-trials.com (ISRCTN59279012).

Selection/inclusion criteria

The study population comprised ambulatory Caucasian men and postmenopausal women (≥ 2 years since last menstruation) ≥ 50 years old with $\text{BMI} < 30 \text{ kg/m}^2$, primary osteoporosis ($\text{BMD } T\text{-score} \leq -2.5 \text{ s.d.}$ at the lumbar spine, femoral neck, or total hip using gender-specific reference populations for Lunar or Hologic dual X-ray absorptiometry devices) and had at least one osteoporotic fracture risk factor (e.g. age > 75 years, prevalent vertebral fracture, family history of osteoporotic fracture, previous low trauma fracture, or known low BMD). All patients had serum $25(\text{OH})\text{D} > 22.5 \text{ nmol/l}$, but randomization was controlled so that 80% of patients had baseline $25(\text{OH})\text{D}$ between 22.5 and 50 nmol/l and 20% had $25(\text{OH})\text{D} \geq 50 \text{ nmol/l}$. Eligible patients also agreed to limit exposure to sunlight (Sun Protection Factor (SPF) ≥ 15 sunscreen was applied if exposure to sunlight was $> 1 \text{ h}$).

Exclusion criteria included uncontrolled active disease (e.g. hypertension, diabetes, HIV, or hepatitis B or C), regular or unavoidable exposure to sunlight (e.g. outdoor work), skeletal diseases (including osteomalacia, Paget's disease, and secondary forms of osteoporosis), documented hypercalciuria without calcium supplementation ($> 10 \text{ mmol/24 h}$), hyper- or hypocalcemia, hyper- or hypoparathyroidism, severe malabsorption (including that induced by gastric surgery), severe renal insufficiency (creatinine clearance $< 30 \text{ ml/min}$), severe liver insufficiency, and history or increased risk of venous thromboembolism.

Patients were also excluded if they had previously taken treatments affecting bone or calcium metabolism or interfering with vitamin D absorption or metabolism without an appropriate washout period before inclusion (vitamin D $> 400 \text{ IU}$ daily in the month before selection, single dose $> 10\,000 \text{ IU}$ in the last 3 months, or single dose $> 50\,000 \text{ IU}$ in the last 12 months; long-term oral (> 8 months) or inhaled (> 6 months) glucocorticoid

treatment in the previous year; calcitriol (1,25-(OH)₂ vitamin D) or 1 α -vitamin D (>0.25 μ g daily) in the previous 6 months). During the study, vitamin D-fortified foods and drinks, calcium and vitamin D (other than those provided), multivitamins and vitamin A, and concomitant treatments interfering with bone, calcium, or vitamin D (such as bisphosphonates, sex hormones, and PTH and derivatives) were also forbidden. For ethical reasons, patients with 25(OH)D $\leq$ 22.5 nmol/l were not included, as vitamin D supplementation was deemed mandatory in these patients.

In order to more thoroughly assess the effect of baseline 25(OH)D on mean increase, another study was conducted in parallel in patients screened with the selection/inclusion criteria of the above-mentioned study, but with baseline 25(OH)D $\leq$ 22.5 nmol/l and thus with vitamin D deficiency. In this open-label study, patients were treated with strontium ranelate 2 g/vitamin D₃ 1000 IU for 1 year. Changes in mean 25(OH)D from baseline were evaluated at 3, 6, and 12 months, and the percentage of these patients with serum level $\geq$ 50 nmol/l at 6 and 12 months was calculated.

Randomization and interventions

Randomization was performed using an interactive voice system. Treatment allocation was stratified by country and baseline serum 25(OH)D level. The unbalanced 4:1 randomization ratio in favor of strontium ranelate 2 g/vitamin D₃ 1000 IU was chosen according to the requirements of sufficient population exposure for the safety assessment of new drugs. Patients were allocated to daily oral administration of strontium ranelate 2 g/vitamin D₃ 1000 IU or strontium ranelate 2 g (one sachet with water at bedtime) for 6 months. Study treatments were identically packaged and labeled, and patients and investigators were blinded to treatment allocation. All patients also received a daily supplement of calcium 1 g. A single-dose vial of vitamin D₃ of 200 000 IU was administered orally as a rescue medication to any patient with 25(OH)D $\leq$ 22.5 nmol/l at 1 or 3 months.

Serum 25(OH)D concentrations were determined from blood samples collected in the morning, at fasting state at selection and at 1-, 3-, and 6-month visits. The samples were analyzed in a central laboratory (Supreme, Liège, Belgium) using a 25(OH)D ¹²⁵I RIA Kit (DiaSorin, Stillwater, MN, USA). Falls, defined as 'unintentionally coming to rest on the ground, floor, or other lower level', were assessed using patients' diaries and recorded at each

visit from inclusion. Adverse event data were collected at every study visit. Other safety data included laboratory parameters, clinical measurements, and physical examination. Blood and urine parameters were analyzed at a central laboratory (BARC, Ghent, Belgium), from morning samples taken at selection, 3, and 6 months. PTH and 1,25-(OH)₂ vitamin D₃ levels were determined from morning blood samples taken at these visits and at 1 month using an N-tact PTH SP IRMA Kit (DiaSorin) and 1,25-dihydroxyvitamin D ¹²⁵I RIA Kit (DiaSorin) respectively. Urine spot samples were collected in the morning, after an overnight fast.

The primary endpoint was circulating serum 25(OH)D concentration, which included 25-hydroxyvitamins D₂ and D₃, at the last post-baseline evaluation over 3 months. Concentration of 25(OH)D at 6 months, physical performance (Short Physical Performance Battery (SPPB) test) after 6 months (27), number of falls, PTH level, serum 1,25-(OH)₂ vitamin D₃, and safety data were secondary endpoints.

Statistical analysis

The randomized set included all patients randomly assigned to therapy. The full analysis set was defined as all patients in the randomized set who took at least one dose of study medication and who had at least one post-baseline 25(OH)D measurement from randomization to 3 months. For the primary efficacy endpoint, estimate of sample size was based on the number of patients who reached 25(OH)D $\geq$ 50 nmol/l after 3 months' treatment with either strontium ranelate 2 g/vitamin D₃ 1000 IU or strontium ranelate 2 g to obtain a between-group difference using a two-sided χ^2 test for the comparison of two percentages at 5% type 1 error. Sample size estimation was, however, superseded by safety data requirements for new drugs. To best fulfill these International Conference of Harmonization requirements (www.ich.org, accessed July 2, 2013), 400 patients on strontium ranelate 2 g/vitamin D₃ 1000 IU and 100 patients on strontium ranelate 2 g were required.

Baseline characteristics are presented as descriptive statistics with numbers and percentages for qualitative data and mean $\pm$ s.d. for quantitative data. The proportion of patients with 25(OH)D levels $\geq$ 50 nmol/l during 3 months (last-observation-carried-forward approach) and at 3 and 6 months (observed cases approach) in each treatment group was compared using a logistic regression model with country, treatment, and baseline 25(OH)D (22.5 nmol/l < 25(OH)D < 50 nmol/l or 25(OH)D

≥ 50 nmol/l) as factors to produce an estimate (E) of the adjusted between-group odds ratio (OR) with associated S.E.M. of the estimate, 95% CIs, and P values. Results are also presented according to baseline 25(OH)D values (from ≥ 22.5 to <50 nmol/l and ≥ 50 nmol/l). Countries with a small number of patients were grouped together to produce a valid statistical model. To correct the analysis for vitamin D rescue, 25(OH)D values obtained following rescue were discarded and substituted with the last pre-rescue value.

Mean change and relative change in 25(OH)D from baseline to 3 and 6 months in each treatment group were compared using a general linear model with country, treatment, and baseline 25(OH)D (for the change only) as factors to produce an estimate of the adjusted between-group means difference with associated S.E.M. of the estimate, 95% CI, and P values. Results of the mean change are also presented according to baseline 25(OH)D values (from ≥ 22.5 to <50 nmol/l and ≥ 50 nmol/l). A general linear model was used to calculate an estimate of the adjusted means difference in relative change in SPPB score as a percentage from baseline to 6 months between the strontium ranelate 2 g/vitamin D₃ 1000 IU and strontium ranelate 2 g groups, with country and baseline vitamin D level as fixed effects. The proportion of patients with falls was compared between treatment

groups using a logistic regression model, which included baseline value of fall (Yes/No) as an additional factor. Adverse events were analyzed in terms of number of events and number and percentage of patients reporting at least one adverse event. Bilateral type 1 error was set at 5%. Statistical analyses were carried out by Atlanstat (Rezé, France) using SAS/PC Software, version 9.1.3.

Results

A total of 1450 patients were screened and 980 were selected for the study. Of the latter, 518 patients were included and randomly assigned: 413 to strontium ranelate 2 g/vitamin D₃ 1000 IU and 105 to strontium ranelate 2 g (Fig. 1). Twenty patients (19 (4.6%) on strontium ranelate 2 g/vitamin D₃ 1000 IU and one (1%) on strontium ranelate 2 g) who lacked a post-baseline 25(OH)D value or who did not take a study treatment from baseline to 3 months were excluded from the full analysis set. Baseline characteristics of the two groups were similar (Table 1). Mean baseline 25(OH)D was 44.1 ± 14.6 nmol/l, and vitamin D spectra were identical in both groups. Treatment duration was 164.3 ± 45.9 days. Compliance was satisfactory in both treatment arms (92 ± 18 vs $94 \pm 16\%$). Vitamin D rescue was needed for ten patients (three in the strontium ranelate 2 g/vitamin D₃ 1000 IU

Figure 1

Trial profile. 25(OH)D, 25-hydroxyvitamin D; BMD, bone mineral density; FAS, full analysis set.

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Table 1 Baseline characteristics. Values are means $\pm$ s.d. or n(%).

	Randomized double-blind 6-month study in patients with vitamin D insufficiency ^a or sufficiency ^b (randomized set: n=518)		Parallel open 12-month study in patients with vitamin D deficiency ^c (included set: n=19)
	Strontium ranelate 2 g/vitamin D ₃ 1000 IU (n=413)	Strontium ranelate 2 g (n=105)	Strontium ranelate 2 g/vitamin D ₃ 1000 IU (n=19)
Demographic characteristics			
Age (years)	66.9 $\pm$ 8.3	66.6 $\pm$ 8.0	65.5 $\pm$ 8.5
Women	372 (90%)	97 (92%)	18 (95%)
Time since last menses (years)	19.5 $\pm$ 9.0	18.6 $\pm$ 8.2	16.4 $\pm$ 8.4
Men	41 (10%)	8 (8%)	1 (5%)
BMI (kg/m ²)	25.3 $\pm$ 3.3	25.0 $\pm$ 3.0	25.9 $\pm$ 2.8
Estimated glomerular filtration rate (ml/min)	77.8 $\pm$ 14.2	76.8 $\pm$ 16.0	78.2 $\pm$ 18.1
Osteoporosis characteristics			
Osteoporosis duration (months)	41.9 $\pm$ 54.5	41.5 $\pm$ 54.7	40.2 $\pm$ 42.4
History of osteoporotic vertebral fracture	48 (12%)	7 (7%)	3 (16%)
History of osteoporotic peripheral fracture	86 (21%)	27 (26%)	4 (21%)
Lumbar L1–L4 T-score	–2.86 $\pm$ 0.84	–2.79 $\pm$ 0.94	–2.76 $\pm$ 1.12
Total hip T-score	–1.75 $\pm$ 0.84	–1.83 $\pm$ 0.81	–1.71 $\pm$ 0.71
Femoral neck T-score	–2.26 $\pm$ 0.72	–2.32 $\pm$ 0.63	–2.34 $\pm$ 0.53
Vitamin D status			
Mean 25(OH)D (nmol/l)	44.0 $\pm$ 14.9	44.4 $\pm$ 13.3	18.8 $\pm$ 1.9
Baseline 25(OH)D < 50 nmol/l	333 (81%)	85 (81%)	19 (100%)
Baseline 25(OH)D $\geq$ 50 nmol/l	80 (19%)	20 (19%)	–
Patients on previous vitamin D-containing treatment	155 (38%)	39 (37%)	5 (26%)
Lifestyle characteristics			
Physical activity (Yes) ^d	274 (66%)	73 (70%)	11 (58%)
Current alcohol consumption (Yes) ^e	95 (23%)	21 (20%)	6 (32%)
Current smoker (Yes) ^f	62 (15%)	11 (11%)	7 (37%)

25(OH)D, serum 25-hydroxyvitamin D.

^aBaseline 25(OH)D $>$ 22.5 and $<$ 50 nmol/l.

^bBaseline 25(OH)D $\geq$ 50 nmol/l.

^cBaseline 25(OH)D $\leq$ 22.5 nmol/l.

^dPhysical activity was assessed via a questionnaire (yes/no/has stopped were possible answers; if yes, activity intensity was classified as occasional, regular, or intensive, and its weekly duration was calculated). Physical activity was occasional for 15.0% of patients, regular for 76.5%, and intensive for 8.5%, with a mean weekly duration of 9.7 $\pm$ 12.5 h in the randomized set.

^eAlcohol consumption and smoking habit were assessed via a questionnaire (yes/no/has stopped were possible answers; if yes, mean consumption duration was assessed and weekly intake was calculated). Mean alcohol consumption duration was 31.9 $\pm$ 14.8 years, with a mean consumption of 5.5 $\pm$ 12.7 units/week in the randomized set.

^fMean smoking duration was 28.1 $\pm$ 14.3 years, with a mean of 13.4 $\pm$ 8.5 cigarettes smoked per day in the randomized set.

group and seven in the strontium ranelate 2 g group), all of whom were successfully corrected after receiving additional vitamin D supplementation and six of whom remained in the study until the end. None withdrew because of treatment failure.

Mean duration since osteoporosis diagnosis was 41.8 $\pm$ 54.5 months, although duration was less than a year in nearly half of patients (47%). A quarter (25%) had a family history of osteoporosis. Peripheral fractures were reported twice as often (22%) as vertebral fractures (11%), but the percentage of patients with two or more of these types of fracture was similar (6 vs 5% respectively). Lower extremity assessment (SPPB) showed that physical function was good in most patients (mean total score of

9.9 $\pm$ 1.9 out of maximum of 12). At inclusion, more than half of patients (54%) had previously taken at least one treatment for osteoporosis that interfered with bone metabolism before the washout period. Controlled hypertension (42%), osteoarthritis (31%), and hypercholesterolemia (24%) were the most common comorbidities, and renin–angiotensin system inhibitors (30%), anti-inflammatory/antirheumatic agents (25%), β -blockers (24%), and lipid-lowering agents (24%) were the most commonly used concomitant medications during the treatment period. Over this period, most patients (86%) took at least one concomitant medication. Serum PTH and calcium levels, and urine calcium levels, were normal in both groups (data not shown).

Correction of vitamin D insufficiency: proportion of patients with 25(OH)D $\geq$ 50 nmol/l

In the whole population ($n=498$), more patients reached serum 25(OH)D levels $\geq$ 50 nmol/l during 3 months with strontium ranelate 2 g/vitamin D₃ 1000 IU (84%) than with strontium ranelate 2 g (44%) ($P<0.001$). A sensitivity analysis taking dropout rate and physiological fluctuation of 25(OH)D into account using the same analysis (observed cases method) produced similar results by 3 months (84 vs 44%; $P<0.001$). The maintenance of efficacy was confirmed by 6 months (observed cases method; 86 vs 40%; $P<0.001$). Comparable results were observed in patients with baseline 25(OH)D >22.5 –50 nmol/l ($n=400$). By 3 months, 82% of the patients treated with strontium ranelate 2 g/vitamin D₃ 1000 IU reached 25(OH)D $\geq$ 50 nmol/l compared with 39% on strontium ranelate 2 g ($P<0.001$). By 6 months, these percentages were 83 vs 29% ($P<0.001$).

In patients with vitamin D deficiency, the efficacy of daily supplementation of 1000 IU vitamin D was assessed in 18 patients with 25(OH)D $\leq$ 22.5 nmol/l treated with strontium ranelate 2 g/vitamin D₃ 1000 IU. Serum 25(OH)D was $\geq$ 50 nmol/l after 12 months in two-thirds (67%) of the patients.

Correction of vitamin D insufficiency: mean change in 25(OH)D from baseline

Corresponding mean changes in 25(OH)D from baseline to 3 and 6 months (observed cases method) were also analyzed in the whole population, and in patients with vitamin D insufficiency (25(OH)D >22.5 –50 nmol/l) at baseline, and patients without vitamin D insufficiency (25(OH)D $\geq$ 50 nmol/l) at baseline ($n=98$). The results of these analyses are presented in Table 2. Moreover, in patients with vitamin D deficiency, mean 25(OH)D increased from baseline (18.7 ± 1.9 nmol/l) to 3 months (57.4 ± 11.1 nmol/l) and remained stable thereafter (54.5 ± 13.1 and 54.4 ± 17.3 nmol/l at 6 and 12 months respectively), with a mean change of 35.9 nmol/l after 6 months and of 35.8 nmol/l after 12 months ($n=16$). Figure 2 shows the mean increase in 25(OH)D at 6 months, according to serum baseline 25(OH)D concentration.

Falls, physical function, 1,25-(OH)₂ vitamin D, and PTH

Regarding falls, 17% (65/394) of patients receiving strontium ranelate 2 g/vitamin D₃ 1000 IU and 20% (21/104) of strontium ranelate 2 g patients experienced at least one post-baseline fall (estimated OR=0.7; 95% CI,

0.4–1.3, NS). Physical function improved in both treatment groups from baseline to 3 and 6 months. After 6 months, SPPB increased from 9.9 ± 1.8 to 10.2 ± 1.8 with strontium ranelate 2 g/vitamin D₃ 1000 IU and from 9.8 ± 2.1 to 10.1 ± 2.0 with strontium ranelate 2 g (between-group difference for relative change E (S.E.M.) = -0.7% (1.9%); 95% CI, -4.5 to 3.1% , NS). The increase in mean 1,25-(OH)₂ vitamin D was higher with strontium ranelate 2 g/vitamin D₃ 1000 IU than with strontium ranelate 2 g after 6 months of treatment (11.5 ± 22.1 vs 0.0 ± 19.0 ng/l; $P<0.001$). Mean intact PTH levels decreased over the same time in both groups: -0.6 ± 1.0 vs -0.4 ± 1.2 pmol/l. No clinically relevant changes over time for either treatment group or between-group differences in vital signs, hematology, or biochemistry parameters were detected, except for a slight increase in serum phosphorus and decrease in serum calcium levels in both groups, as expected according to the mechanism of action of strontium ranelate (data not shown).

Adverse events

Both strontium ranelate 2 g/vitamin D₃ 1000 IU and strontium ranelate 2 g were well tolerated. After 6 months, the proportion of adverse events related to treatment was 15% in both groups, most commonly gastrointestinal disorders. Serious adverse events occurred in 21 (5%) patients on strontium ranelate 2 g/vitamin D₃ 1000 IU and nine (9%) patients on strontium ranelate 2 g. No venous thromboembolism was reported, and there was one case of nonfatal myocardial infarction in the strontium ranelate 2 g/1000 IU group. A single death (congestive heart failure) in the strontium ranelate 2 g group was not considered to be treatment related. Hypercalciuria based on a spot urine test was reported as an adverse event in 28 patients (7%) on strontium ranelate 2 g/vitamin D₃ 1000 IU vs three patients (3%) on strontium ranelate 2 g and was not associated with any clinically significant symptoms. Elevated urinary calcium:creatinine ratio values were reported in 12% of patients on strontium ranelate 2 g/vitamin D₃ 1000 IU and 9% of patients on strontium ranelate 2 g. A slight decrease in serum calcium with no clinical relevance was observed similarly in the two treatment groups (-0.1 ± 0.1 mmol/l). Conversely, a slight increase in blood phosphorus of the same order of magnitude was detected. High, potentially clinically significant, abnormal blood calcium values (>2.64 mmol/l) were reported in 1% of patients in both groups, though none of these cases was associated with renal lithiasis or other symptoms of vitamin D intoxication. Four patients in the strontium ranelate 2 g/vitamin D₃

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Table 2 The mean change in 25(OH)D from baseline to 3 months and from baseline to 6 months (observed cases) in the whole population ($n=498$) and subpopulations with^a ($n=400$) or without^b ($n=98$) vitamin D insufficiency at baseline, according to a 50 nmol/l threshold. Values are presented as mean $\pm$ s.d. or percentage. Numbers in parentheses show numbers in each group.

	Mean change in 25(OH)D (nmol/l)		E; 95% CI; P value
	Strontium ranelate 2 g/vitamin D ₃ 1000 IU	Strontium ranelate 2 g	
3-month results ^c			
Overall population	21.1 $\pm$ 18.9 ($n=378$)	5.3 $\pm$ 19.1 ($n=98$)	15.7; 12.1–19.4; $P<0.001$
Patients with vitamin D insufficiency at baseline ^a	25.1 $\pm$ 17.0 ($n=305$)	8.7 $\pm$ 18.0 ($n=80$)	15.8; 11.7–19.9; $P<0.001$
Patients with no vitamin D insufficiency at baseline ^b	4.7 $\pm$ 17.3 ($n=73$)	–9.9 $\pm$ 16.8 ($n=18$)	15.6; 7.2–24.0; $P<0.001$
6-month results ^c			
Overall population	22.8 $\pm$ 17.8 ($n=358$)	1.1 $\pm$ 15.4 ($n=95$)	21.6; 17.9–25.3; $P<0.001$
Patients with vitamin D insufficiency at baseline ^a	24.4 $\pm$ 17.7 ($n=289$)	1.2 $\pm$ 15.4 ($n=77$)	22.5; 18.5–26.6; $P<0.001$
Patients with no vitamin D insufficiency at baseline ^b	16.3 $\pm$ 16.7 ($n=69$)	0.5 $\pm$ 15.9 ($n=18$)	15.8; 7.7–24.0; $P<0.001$

E, estimate of adjusted means difference between strontium ranelate 2 g/vitamin D₃ 1000 IU–strontium ranelate 2 g and 95% CI of the estimate and corresponding P value; 25(OH)D, serum 25-hydroxyvitamin D.

^a25(OH)D >22.5 – <50 nmol/l.

^b25(OH)D ≥ 50 nmol/l.

^cUsing an observed cases statistical method to analyze results from baseline to time point.

1000 IU group had 25(OH)D ≥ 125 nmol/l at 6 months, but none of these reports was associated with safety concerns.

Discussion

The combination of strontium ranelate 2 g and vitamin D₃ 1000 IU was effective at correcting vitamin D insufficiency, with 86% of osteoporotic patients with vitamin D insufficiency reaching a 25(OH)D ≥ 50 nmol/l threshold. The percentage of patients with corrected vitamin D levels after 3 months increased in strontium ranelate 2 g/vitamin D₃ 1000 IU compared with strontium ranelate 2 g ($P<0.001$). There was also a significant between-group difference in mean increase of 25(OH)D in favor of strontium ranelate 2 g/vitamin D₃ 1000 IU ($P<0.001$). Physical performance improved in both treatment groups. Both treatments were generally well tolerated. Adverse events were as expected in a population of elderly osteoporotic patients treated with strontium ranelate. Their nature and frequency were similar in both treatment groups, and no unexpected safety concern was raised. Combining vitamin D₃ with an osteoporosis treatment safely corrects vitamin D insufficiency in osteoporosis (28, 29).

The dosage of vitamin D in a supplement required to reach a given 25(OH)D threshold depends on baseline vitamin D values in the population studied (30). The increase in 25(OH)D levels in patients in our study was inversely proportional to baseline levels (Fig. 2).

The benefits of vitamin D supplementation are dose dependent (31). Levels of 25(OH)D have been shown to rise by an average of 1.7 nmol/l in healthy individuals with a mean baseline 25(OH)D of 70 nmol/l for every 100 IU of vitamin D supplementation (32) and by an average of 2.8 nmol/l for every 100 IU in healthy individuals with a mean 25(OH)D baseline value of 40.7 nmol/l (33). As expected, 25(OH)D levels in the strontium ranelate 2 g/vitamin D₃ 1000 IU group rose from 44.2 to 66.9 nmol/l after 6 months. Generally, 25(OH)D levels with strontium ranelate 2 g did not change (small fluctuations observed during the study may have been caused by seasonal exposure to sunlight: 91% of 3-month visits occurred from June to September).

Comparison of the increase in mean 25(OH)D with daily strontium ranelate 2 g/vitamin D₃ 1000 IU, observed in another trial of an osteoporosis treatment/vitamin D₃ fixed-dose combination, illustrates the dose dependency of response to vitamin D supplementation (28). Treatment of vitamin D insufficiency in postmenopausal osteoporosis with the equivalent of vitamin D₃ 800 IU/day, via a weekly fixed-dose combination of alendronate 70 mg/vitamin D₃ 2800 IU plus a weekly vitamin D₃ 2800 IU single-tablet supplement, increased 25(OH)D levels by 15.2 nmol/l (95% CI, 13.0–17.5 nmol/l) over 39 weeks (28). The control group received the equivalent of vitamin D₃ 400 IU/day, through weekly alendronate 70 mg/vitamin D₃ 2800 IU plus placebo, and the corresponding

Figure 2

Mean increase in 25(OH)D from baseline to 6 months with strontium ranelate 2 g/vitamin D₃ 1000 IU or strontium ranelate 2 g, according to baseline 25(OH)D status: vitamin D deficient (≤ 22.5 nmol/l)*, vitamin D insufficient (22.5 nmol/l $<$ 25(OH)D $<$ 50 nmol/l), and sufficient vitamin D (25(OH)D ≥ 50 nmol/l). 25(OH)D, serum 25-hydroxyvitamin D. *Result from the parallel open 12-month study. Analysis performed using observed cases method.

increase in 25(OH)D levels was 10.0 nmol/l (95% CI, 7.8–12.0 nmol/l). However, with strontium ranelate 2 g/vitamin D₃ 1000 IU daily, the increase in 25(OH)D levels was 21.6 nmol/l (95% CI, 17.9–25.3 nmol/l) after 6 months in the study population.

Vitamin D insufficiency can further reduce bone strength in osteoporosis, as well as attenuating the efficacy of osteoporosis therapy (1, 34). The use of a fixed-dose combination would address both problems. Fixed-dose combinations could also simplify medication regimens in osteoporosis and improve compliance, as well as enabling greater flexibility with calcium supplementation (35, 36). The summary of product characteristics of strontium ranelate lists no interaction with vitamin D (www.ema.europa.eu/ema, accessed January 21, 2013).

As expected, a 1000 IU daily dosage of vitamin D₃ was safe, regardless of baseline 25(OH)D. A slight increase in serum phosphorus and decrease in serum calcium of no clinical significance were found as previously reported with strontium ranelate (24, 25, 26).

As the safety margin of vitamin D is large (32, 37), vitamin D treatment is unlikely to require regular monitoring. In fact, a recent benefit-risk assessment of vitamin D supplementation in randomized controlled

trials found that doses higher than the daily 1000 IU dose given in this study are safe: patients given daily oral vitamin D (1800–4000 IU) achieved mean 25(OH)D levels of 75–110 nmol/l without adverse events (38). Four patients in our study had 25(OH)D ≥ 125 nmol/l, a suggested dietary tolerability upper limit (39), at 6 months, with no abnormal clinical signs or symptoms.

Generally, the side-effect profile observed with the strontium ranelate 2 g/vitamin D₃ 1000 IU combination was similar to that of strontium ranelate alone. A recent report of an increase in myocardial infarction in patients treated with strontium ranelate led to a new contraindication of the agent in patients with cardiovascular disease (40). One case of nonfatal myocardial infarction was reported in the 512 patients exposed to strontium ranelate in our study.

Time of year in vitamin D studies can be a factor because of endogenous vitamin D production in sun-exposed skin. Appropriate patient selection and measures to attenuate bias from endogenous vitamin D, i.e. randomization, short recruitment period, and use of sun protector, reduced the impact of season on results, though patient compliance to sunscreen was not assessed. Dietary habits might also have affected vitamin D, even though vitamin D-fortified food and drinks were forbidden. Food in general, however, is not recognized as a major source of vitamin D and contributes little to daily vitamin D intakes. Because responder rate was a binary criterion, it could not capture physiological variability in 25(OH)D related to food intake, patient lifestyle, level of outdoor activity, and season (7). The efficacy of strontium ranelate in osteoporosis was not reported here, but its anti-fracture efficacy has been fully established elsewhere in vitamin D-replete patients (24, 25).

Conclusion

This study shows the efficacy and safety of fixed-dose combination of strontium ranelate 2 g/vitamin D₃ 1000 IU for the correction of vitamin D insufficiency in osteoporotic patients with vitamin D insufficiency over 3 months and the maintenance of correction after 6 months. This fixed-dose combination provides osteoporotic patients with high-dose (>800 IU) vitamin D supplementation on a daily basis, which has been shown to be efficacious and safe compared with less-frequent vitamin D-administration or smaller dose regimens.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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