

The effect of prior bisphosphonate therapy on the subsequent therapeutic effects of strontium ranelate over 2 years

E. T. Middleton · S. A. Steel · M. Aye · S. M. Doherty

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Abstract

Summary Many osteoporotic women prescribed strontium ranelate have previously received bisphosphonates. Prior bisphosphonate use blunted the spinal bone mineral density (BMD) response for 6 months. Hip BMD was blunted to a degree for 2 years, although there was an overall increase in hip BMD in contrast to the heel where BMD did not increase.

Introduction Many osteoporotic women commenced on strontium ranelate have already received treatment with bisphosphonates. This study investigates whether prior bisphosphonate use impairs the subsequent therapeutic response to strontium ranelate.

Methods Women were recruited who were either bisphosphonate naïve or currently receiving a bisphosphonate. All women received strontium ranelate and were followed up for 2 years.

Results One hundred and twenty women were recruited. After 2 years, the bisphosphonate-naïve group had significant BMD increases of 8.9%, 6.0% and 6.4% at the spine, hip and heel, respectively. In the prior bisphosphonate group, BMD increased significantly at the spine (4.0%) and hip (2.5%) but not at the heel. At all time points at all sites, the BMD increase was greater in the bisphosphonate-naïve group. BMD at the spine did not increase during the first 6 months in the prior bisphosphonate group but then increased in parallel with the bisphosphonate-naïve group. In contrast, the difference between the two groups in hip

BMD continued to increase throughout the 2 years. P1NP was suppressed in the prior bisphosphonate group for the first 6 months.

Conclusions After bisphosphonate exposure, the BMD response to strontium ranelate is blunted for only 6 months at the spine. At the hip, a degree of blunting was observed over 2 years, although there was an overall increase in hip BMD in contrast to the heel where no increase in BMD was observed.

Keywords Bisphosphonate · Bone mineral density · Osteoporosis · Strontium ranelate

Introduction

Strontium ranelate has been demonstrated to reduce the incidence of vertebral and non-vertebral fractures in postmenopausal women [1, 2]. These fracture prevention trials involved treatment-naïve women; however, in clinical practice, many women who commence strontium ranelate have already received treatment with bisphosphonates. This is certainly the case in the UK where bisphosphonates are the recommended first-line treatment for osteoporosis unless contraindicated [3]. Even after their discontinuation, bisphosphonates continue to suppress bone turnover [4], and this may have consequences on the response to subsequent treatments for osteoporosis.

We have previously reported that women with prior bisphosphonate exposure have a blunted bone mineral density (BMD) response to strontium ranelate for 6 months at the spine and for 1 year at the hip and heel [5]. We believe that this is mostly due to reduced strontium uptake into the skeleton as strontium is almost exclusively

E. T. Middleton (✉) · S. A. Steel · M. Aye · S. M. Doherty
Centre for Metabolic Bone Disease, Hull Royal Infirmary,
Brocklehurst Building, 220-236 Anlaby Road,
Hull HU3 2RW, UK
e-mail: etmiddleton@doctors.org.uk

deposited in newly formed bone tissue [6] and prior bisphosphonate use reduces bone turnover leading to reduced new bone formation. Furthermore, it has been suggested that strontium ranelate alters the balance of bone turnover in favour of bone formation and therefore may have anabolic properties leading to increased amounts of bone tissue [7]. This potentially provides a second mechanism by which prior bisphosphonate use may blunt the BMD response to strontium ranelate as has previously been demonstrated with anabolic therapy [8, 9].

As we have reported a blunting of the BMD response to strontium ranelate in women with prior bisphosphonate use, it is important to know for how long this blunting persists. This is particularly important at the hip and heel where blunting was seen throughout the first year of treatment with strontium ranelate. In this article, we report the results of a second year extension to our original study which aimed to investigate the long-term effects of prior bisphosphonate use on the subsequent therapeutic response to strontium ranelate.

Materials and methods

Year 1

A detailed description of the design of the first year of this study has already been reported [5]. To summarise, postmenopausal women aged 50–80 with either a T-score of less than -2.5 at the hip/spine or a T-score of -2.0 and one other risk factor for fracture were recruited if they were either bisphosphonate naive or currently being treated with a bisphosphonate for more than 1 year. Women were excluded if they had received prior treatment with strontium ranelate, were unable to give informed consent or could not be reliably assessed by dual-energy X-ray absorptiometry (DXA), or if they had medical conditions associated with bone disease. All women gave written informed consent. All women received strontium ranelate 2 g once a day after a 2-h fast and 1.2 g calcium and 800 IU vitamin D daily (Adcal D3). Women were followed up at 3, 6 and 12 months. BMD was measured at the spine (L2–L4) and hip (total hip) by DXA (Lunar Prodigy, GE Lunar, Madison, WI, USA). Heel (right os calcis) BMD was also measured (Lunar Pixi, GE Lunar, Madison, WI, USA). Bone turnover was assessed using procollagen type 1 amino terminal propeptide (P1NP; Elecsys 2010, Roche diagnostics, IN, USA). A DXA-based vertebral fracture assessment (VFA) was performed at baseline and 12 months to look for vertebral fractures. As described previously, a vertebra was considered to be fractured if the VFA deformity grade was moderate or severe [10].

Year 2

All women completing the first year were invited to enter into the second year extension phase of this study. At the 12-month visit, those women wishing to enter into the extension phase were enrolled after given written informed consent. They then continued treatment with strontium ranelate 2 g once a day and Adcal D3 and were followed up at 18 and 24 months using BMD at the spine, hip and heel and P1NP. After 24 months, a further VFA was performed to detect any incident vertebral fractures occurring in the second year. Compliance was calculated at each visit based on returned medications.

As in the first year of the study, the primary end points were the between-group and the within-group changes in axial BMD over the 24 months of the study. Lumbar spine BMD (L2–L4) was used for analysis; however, if there was a prevalent fracture at baseline or an incident fracture during the 2 years of the study in one of these vertebrae, then the fractured vertebra was excluded from the analysis. At the hip, total hip BMD was used for the analysis as this region of interest demonstrates the greatest increase in hip BMD in response to strontium ranelate [1, 2] and is the recommended region of interest for assessing treatment response at the hip [11]. Precision at our centre, as percent coefficient of variation, has been determined using repeat measures in 36 postmenopausal women as 0.9% at spine and 1.0 for the total hip region [12]. The secondary end points were change in heel BMD, the change in P1NP and fracture incidence.

Data analysis

All 108 women who made up the study population from the first year were included in the second year analysis. Initially, the Kolmogorov–Smirnov test for normality was used to assess the distribution of the data. Baseline characteristics were compared between the groups using either a two-sample *t* test or Mann–Whitney *U* test depending on the distribution of the data. Fisher's exact test was used for categorical baseline data.

Changes from baseline for BMD spine, hip and heel and absolute P1NP values at all time points were analysed using mixed modelling to allow for missing data. In the mixed modelling, measurements were assumed to have an autoregressive correlation structure, in which the correlation between measurements on the same patient decreases as the time interval increases. All *p* values reported from the mixed modelling for within-group and between-group comparisons were obtained by applying *t* tests to the estimated means or mean changes at each time point. The between-group comparisons were subsequently repeated after adjusting for baseline differences between the groups.

The significance level chosen was 0.05. The program package used was SPSS for Windows (version 16.0 SPSS, Inc., Chicago, IL).

Study approval, conflict of interest and funding

For both the first year and the extension phase, ethical approval was obtained from the Hull and East Riding Local Research Ethics Committee. The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Clinical trial authorisation was obtained from the Medicines and Healthcare products Regulatory Agency, UK (EudraCT number 2005-003138-16). Servier Laboratories provided the strontium ranelate and a grant to fund the study. ProStrakan provided Adcal D3 as the calcium supplement but no financial support. Servier has paid speaker fees to Dr E Middleton (<£1,000) and Dr M Aye (<£2,000). All authors have no other conflicts of interest. The study design, the data collection, analysis and interpretation, and the manuscript were all carried out by the authors independent of Servier and ProStrakan. All authors had full access to the data and were involved in the manuscript preparation.

Results

Subjects and baseline demographics

One hundred and twenty women were recruited, 60 to each group, of which 12 discontinued prior to the first visit. Therefore, 108 women (52 prior bisphosphonate and 56 bisphosphonate naïve) had follow-up data, and these women made up the study population. One hundred and five women completed the first year of which 97 entered into the second year. Three women discontinued at the 18-month visit resulting in 94 women completing the whole 2 years of the study (45 prior bisphosphonate and 49 bisphosphonate naïve).

The prior bisphosphonate group was older (66.9 vs. 62.5 years, $p=0.001$) and had a lower baseline BMD at the spine (0.799 vs. 0.835 g/cm², $p=0.02$) than the bisphosphonate-naïve group. The prior bisphosphonate group also had a lower baseline P1NP consistent with recent antiresorptive therapy. There were no other significant differences between the groups. The baseline demographics of the 108 women in the study population are summarised in Table 1. In the prior bisphosphonate group, the mean (SD) duration of bisphosphonate use was 64.3 (38.5) months. Details of prior bisphosphonate usage are contained in Table 2.

Compliance was similar in both groups. The mean level of compliance with strontium ranelate in the bisphosphonate-

naïve and prior bisphosphonate groups, respectively, was 95.6% and 95.0% in the first year, and 93.2% and 94.5% in the second year.

Change in spine BMD with strontium ranelate

Over the 2 years of the study, spine BMD increased both in bisphosphonate-naïve women (+8.9%, 0.074 g/cm², $p<0.001$) and in women with prior bisphosphonate exposure (+4.0%, 0.032 g/cm², $p<0.001$). Within the bisphosphonate-naïve group, there was a significant increase in spine BMD after 6-month treatment with strontium ranelate (6-month change: 0.019 g/cm², $p=0.002$). In contrast, the prior bisphosphonate group experienced no significant increase in BMD by 6 months, and a statistically significant increase in spine BMD was only achieved after 12 months of therapy (12-month change: 0.019 g/cm², $p=0.008$).

At all time points, the change in spine BMD from baseline was significantly greater in the bisphosphonate-naïve group than the prior bisphosphonate group, and the difference persisted after adjusting for baseline differences in age and BMD. The difference between the two groups in terms of change in spine BMD was 0.022 g/cm² at 6 months, and by 24 months, the difference had increased to 0.042 g/cm². However, this increase in difference between the groups with time was not significant ($p=0.168$). The change from baseline in spine BMD in each group is reported in Fig. 1a.

Change in hip BMD with strontium ranelate

After 2 years of treatment with strontium ranelate, total hip BMD had increased significantly in both the bisphosphonate-naïve group (0.047 g/cm², 6.0%, $p<0.001$) and the prior bisphosphonate group (0.019 g/cm², 2.5%, $p<0.001$). Within the bisphosphonate-naïve group, the change from baseline in total hip BMD was significant after 6 months (6-month change: 0.014 g/cm², $p<0.001$). In the prior bisphosphonate group, there was no significant change in total hip BMD at 6 months, and by 12 months, the increase in hip BMD from baseline was only just significant (12-month change: 0.006 g/cm², $p=0.048$).

At all time points, the change in total hip BMD from baseline was significantly greater in the bisphosphonate-naïve group than the prior bisphosphonate group, and the difference persisted after adjusting for baseline differences in age and BMD. Over the 2 years of the study, the difference between the two groups in terms of change in total hip BMD increased from 0.013 g/cm² at 6 months to 0.028 g/cm² at 24 months. This progressive increase in difference between the groups with time was statistically significant ($p=0.036$). The change from baseline in total hip BMD in each group is reported in Fig. 1b.

Table 1 Baseline characteristics of the study population

	Prior bisphosphonate <i>n</i> =52	Bisphosphonate naïve <i>n</i> =56	<i>p</i> value
Age (years)	66.9 (6.8)	62.5 (6.8)	0.001 ^a
Menopause age (years)	46.8 (6.0)	47.3 (6.1)	0.68
BMI (kg/m ²)	24.3 (3.5)	24.9 (3.4)	0.37
Current smoking (<i>n</i>)	4 (7.7%)	7 (12.5%)	0.53
Alcohol (U/week)	3.5 (4.7)	5.4 (9.0)	0.63
Prior steroid use (<i>n</i>)	4 (7.7%)	5 (8.9%)	1
Positive family history (<i>n</i>)	16 (30.8%)	15 (26.8%)	0.68
Vertebral fracture on VFA, (<i>n</i>)	15 (28.8%)	10 (17.9%)	0.25
Prior non-vertebral fracture, (<i>n</i>)	24 (46.2%)	26 (46.4%)	1
Vitamin D (nmol/l)	71.9 (26.6)	72.9 (31.1)	0.86
Parathyroid hormone (μg/l)	32.3 (11.4)	31.4 (10.4)	0.66
BMD spine (g/cm ²)	0.799 (0.08)	0.835 (0.08)	0.02 ^a
BMD total hip (g/cm ²)	0.751 (0.11)	0.780 (0.11)	0.18
BMD heel (g/cm ²)	0.369 (0.09)	0.391 (0.07)	0.15
P1NP (μg/l)	30 (13.9)	54 (18.9)	<0.001 ^a

Numbers are *n* (%) or mean (SD)

^a Significant difference between groups

Change in heel BMD with strontium ranelate

Within the bisphosphonate-naïve group, there was a significant increase in heel BMD after 6 months of treatment with strontium ranelate (6-month change: 0.011 g/cm², $p < 0.001$), and after 2 years, heel BMD had increased by a total of 6.4% (0.025 g/cm², $p < 0.001$). There was no significant increase in heel BMD after 2 years of treatment with strontium ranelate in the prior bisphosphonate group. The change from baseline in heel BMD in each group is reported in Fig. 1c.

Change in P1NP in response to strontium ranelate

At baseline, P1NP was significantly lower in the prior bisphosphonate group consistent with recent antiresorptive therapy. In the prior bisphosphonate group, P1NP increased by 43% over the 24 months (30 μg/l to 43 μg/l, $p < 0.001$). In the bisphosphonate-naïve group, P1NP reduced by 17% (54 μg/l to 46 μg/l, $p = 0.003$). The difference in P1NP between the groups was still significant at 3 months (49 vs.

39 μg/l, $p = 0.004$), but by 6 months, P1NP was similar in both groups (48 vs. 42 μg/l, $p = 0.132$) and remained similar for the rest of the 2-year period. Adjusting P1NP for the baseline difference in age did not alter the results. Change in P1NP in response to strontium ranelate is demonstrated in Fig. 2.

Fracture incidence during therapy with strontium ranelate

During the second year of the study, eight women in the prior bisphosphonate group suffered a total of nine incident vertebral fractures between them (four graded as severe on VFA and five as moderate) compared to two women in the bisphosphonate-naïve group (two severe). Non-vertebral fractures occurred in two women in the bisphosphonate-naïve group (wrist and metacarpal) and two women in the prior bisphosphonate group (wrist and rib). Fracture incidence over the 2 years is summarised in Table 3.

Discussion

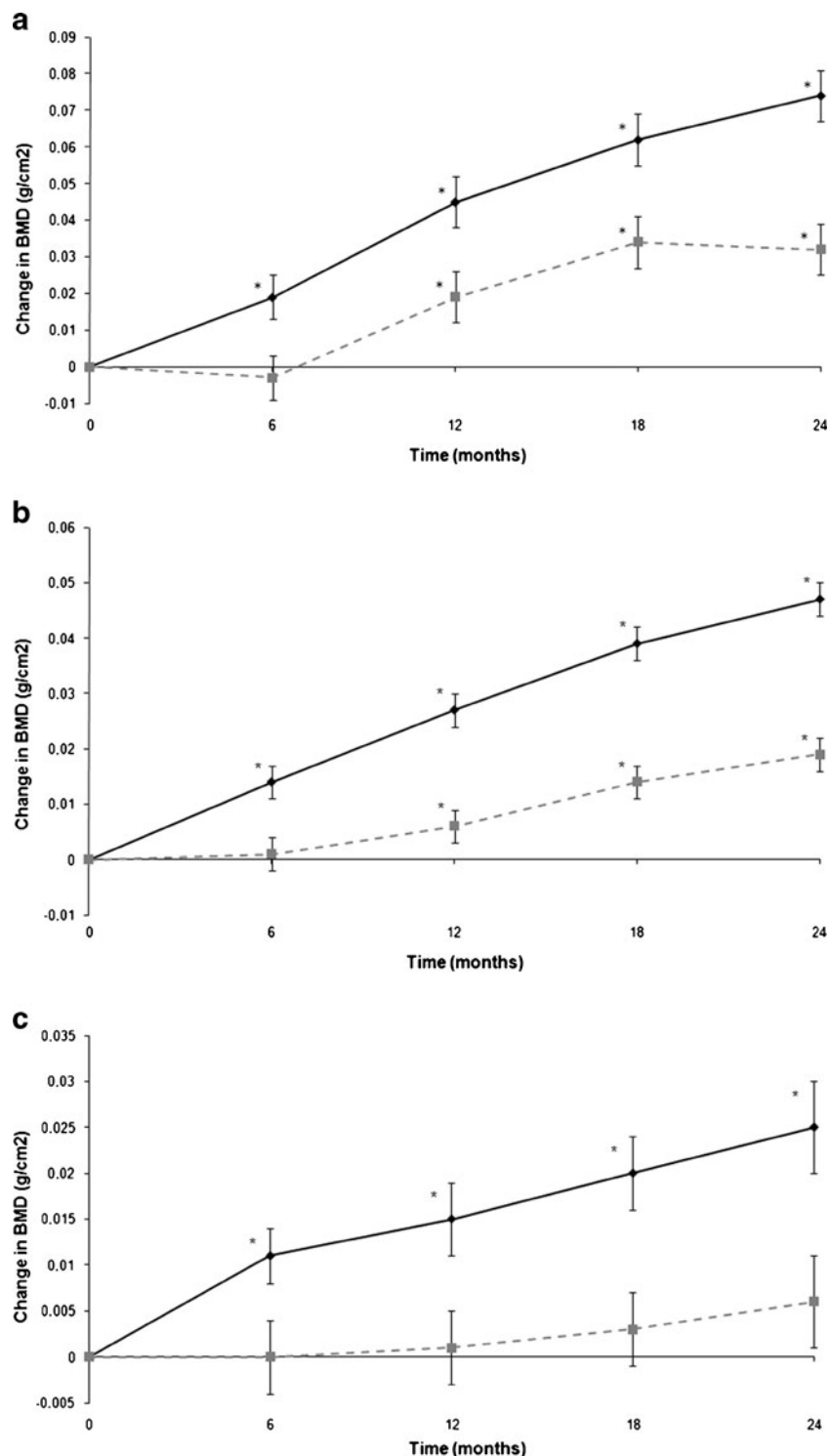
This study provides data on the effect of prior bisphosphonate use on the subsequent bone response to treatment with strontium ranelate. The extension phase of this study demonstrates that the difference in BMD gain between the two groups reported in the first year of the study persists during the second year with no evidence of “catch up” by the prior bisphosphonate group. In this study, the gains in BMD in the bisphosphonate-naïve group were similar to those observed in the SOTI study [1], suggesting that the difference between the groups was due to a reduction in BMD gain in the prior bisphosphonate group.

During treatment with strontium ranelate, strontium is only deposited into new bone packets formed during the

Table 2 Bisphosphonate usage in the prior bisphosphonate group immediately prior to strontium ranelate and previous exposure

	Ever used		Immediately prior	
	Number	Percentage	Number	Percentage
Alendronate	39	75	27	51.9
Risedronate	29	55.8	24	46.2
Ibandronate	1	1.9	1	1.9
Didronel	15	28.8	0	0
Pamidronate	1	1.9	0	0

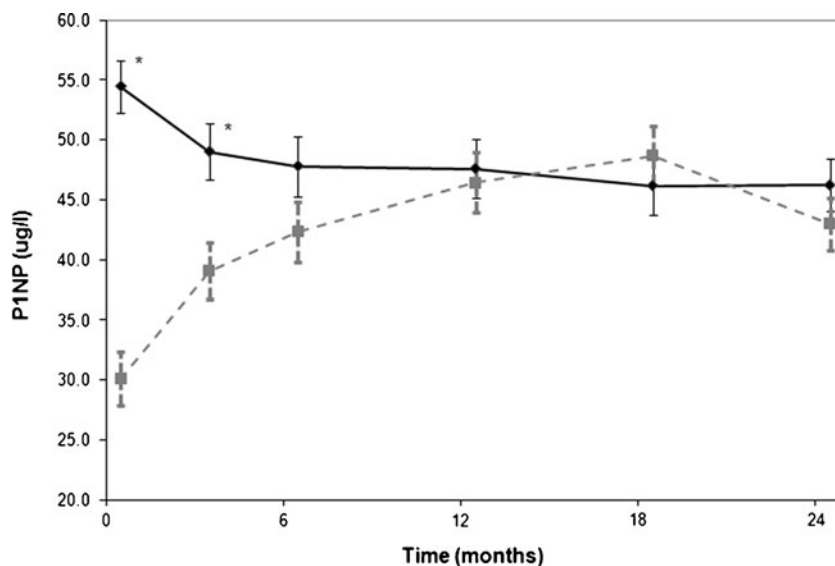
Fig. 1 Mean change from baseline (\pm SE) in BMD at the lumbar spine (a), total hip (b) and heel (c) in response to treatment with strontium ranelate in bisphosphonate-naive women (solid line) and in women with prior bisphosphonate exposure (broken line). Asterisks significant increase from baseline



treatment period [6, 13]. This induces large increases in BMD as strontium's high atomic number leads to greater X-ray attenuation than calcium. Biopsy studies suggest that the average bone strontium content after 2 years of treatment is around 1% [13]. A bone strontium content of 1% causes a 10% increase in BMD [14] which would be consistent with the 9% increase in BMD observed in the

bisphosphonate-naive group in this study. The blunted BMD response observed in the prior bisphosphonate group is therefore likely to result from reduced strontium uptake in to the bone due to a reduced number of new bone packets caused by the prolonged suppression of bone turnover following bisphosphonate therapy [4]. A second potential mechanism for the blunting of the BMD

Fig. 2 Change in mean (\pm SE) P1NP in response to strontium ranelate in bisphosphonate-naïve women (*solid line*) and in women with prior bisphosphonate exposure (*broken line*). Asterisks significant difference between groups



response is provided by evidence that strontium ranelate may alter the balance of bone turnover in favour of bone formation which in turn may lead to an increase in the overall amount of bone tissue [7, 15, 16]. If this is correct, then prior bisphosphonate therapy may also diminish these anabolic actions as has been previously reported for teriparatide [8, 9].

At the spine, there was no increase in BMD in the prior bisphosphonate group during the first 6 months of therapy which led to a significant difference between the two groups at 6 months. Although this difference in BMD persisted for the remainder of the study, there was no further significant increase in the difference, suggesting that after 6 months, the two groups gained BMD at a similar rate. It would therefore appear that the blunting of the BMD response at the spine only lasts for approximately 6 months after the discontinuation of bisphosphonate therapy. This would be consistent with the observation that bone turnover, as measured by P1NP, was suppressed in the prior bisphosphonate group for 3 to 6 months after which bone turnover remained similar between the two groups.

The second year extension of this study demonstrated that hip BMD had increased significantly by 2 years. This confirms that the hip is capable of responding to strontium ranelate after the discontinuation of bisphosphonates. However, in contrast to the spine, the magnitude of the difference between the two groups in terms of hip BMD continued to increase at each visit, and this continued divergence was statistically significant. This suggests that in the prior bisphosphonate group, BMD is gained at a slower rate at the hip throughout the 2 years. The more prolonged blunting at the hip may arise as the hip, unlike the spine, is predominantly cortical bone. Cortical bone is less metabolically active than trabecular bone [17] and as such may take longer to overcome the bisphosphonate-induced suppression of bone turnover. Furthermore, it has been suggested in animal studies that the preferential incorporation of strontium ions into newly formed bone packets, as opposed to older bone packets, is greater in cortical than trabecular bone [18]. Therefore, any reduction in the rate of bone turnover would lead to a greater impedance of strontium uptake into cortical bone than trabecular bone.

Table 3 Fractures occurring during 2 years of treatment with strontium ranelate

	Number of women suffering a fracture in year 1		<i>p</i> value
	Bisphosphonate naïve <i>n</i> =56	Prior bisphosphonate <i>n</i> =52	
Any fracture	3	12	0.014
Vertebral fractures	2	8	0.047
Non-vertebral fractures	1	4	0.194
Number of women suffering a fracture in year 2			
	Bisphosphonate naïve <i>n</i> =50	Prior bisphosphonate <i>n</i> =47	
Any fracture	4	10	0.084
Vertebral fractures	2	8	0.047
Non-vertebral fractures	2	2	1.000

At the heel, the blunting of the BMD response to strontium ranelate seems even greater. In the prior bisphosphonate group, 2 years of treatment failed to increase BMD at the heel significantly compared to an increase of 6.4% in the bisphosphonate-naïve group. Like the spine, the heel is predominantly a trabecular bone site so it is interesting that prior bisphosphonate exposure results in the two sites responding so differently to the strontium ranelate. As we have previously hypothesised [5], the difference in duration of blunting may be due to the heel containing predominantly yellow bone marrow, while the spine is a red bone marrow site [19]. Osteoclasts, osteoblasts and various key cytokines involved in bone turnover are derived from the red bone marrow [20], and the relative lack of these at yellow bone marrow sites may prolong the bisphosphonate-induced suppression of bone turnover and thus the blunting of the BMD response to strontium ranelate.

Overall, it appears that the effect of prior bisphosphonate exposure on the response to strontium ranelate depends on the skeletal site studied with only a short duration of blunting at the spine, more prolonged blunting at the hip and the most profound blunting occurring at the heel. If the blunting of the BMD response is predominantly due to reduced strontium uptake into new bone packets [6] resulting from suppressed bone turnover, then this study may provide interesting insights into how different areas of the skeleton recover after the withdrawal of bisphosphonates. To date, studies looking at the withdrawal of bisphosphonates use bone markers to assess the recovery of bone turnover [4]. However, bone markers only provide information on the rate of bone turnover in the skeleton as a whole with areas of greater bone turnover, such as the spine, contributing to the majority of the total level of bone marker.

In a recently published study, Busse et al. [21] reported the effects of strontium ranelate on 15 paired bone biopsy specimens obtained from the iliac crest of women with prior bisphosphonate exposure. This study is unique as the use of paired bone biopsies enables longitudinal assessment of the effects of strontium ranelate on bone tissue. This study demonstrated that bone strontium content increased after both 6 and 12 months of therapy. However, while there was an increase in bone strontium content, the lack of a bisphosphonate-naïve control group makes it unclear whether the increase observed was diminished at all by the prior bisphosphonate use. Busse et al. also reported that, in women with prior bisphosphonate exposure, bone volume and trabecular thickness did not increase during the first 6 months of therapy with strontium ranelate, but significant increases in these parameters occurred after 12 months. This is consistent with our results which demonstrate that the blunting of the BMD response to strontium ranelate

wears off at the spine after 6 months. As the iliac crest is a trabecular bone site, the study by Busse et al. does not provide any information on the changes in cortical bone where, in the present study, more prolonged blunting was observed.

This study investigates switching therapy from bisphosphonates to strontium ranelate. There are relatively few studies assessing the topic of switching therapy, although this is a frequent occurrence in clinical practice. This is an area which needs more research as the number of different treatments for osteoporosis increases. Switching between antiresorptives is unlikely to have major implications for the efficacy of the new therapy as the overall effects on bone are the same. In fact, studies demonstrate that switching from alendronate to denosumab [22] leads to further reductions in bone turnover, although it is still to be proven whether this confers any clinical benefits in terms of fracture reduction and there is even a possibility that prolonged over suppression of bone may be harmful [23]. For anabolic therapy, it has been demonstrated that prior oral bisphosphonate use inhibits the gains in BMD at the spine over the whole 2 years of treatment with teriparatide, while at total hip, BMD does not increase significantly during the first year of therapy [8, 9]. Finally, the present study has demonstrated that prior bisphosphonate use blunts the BMD response to strontium ranelate, although at the spine at least, this blunting appears to wear off as the antiresorptive efficacy of the bisphosphonate declines over time. Therefore, in clinical practice, careful consideration is needed when considering which initial treatment to use, with the choice of agent tailored for the individual patient, and when considering whether or not to switch class of treatment.

The most important issue regarding osteoporosis treatment is not the effect on BMD but the effect on fracture incidence. It is difficult to predict how the bisphosphonate-induced blunting of the BMD response to strontium will affect the ability of strontium ranelate to reduce fracture incidence. If strontium uptake into the skeleton is reduced, then it is plausible that this will reduce the effect of strontium on bone strength. However, it is also likely that prior bisphosphonate therapy will have a period of residual effect on fracture risk [4] which may provide protection during the transition period. This study demonstrated an increased incidence of vertebral fracture in those women with prior bisphosphonate exposure in both the first and second year. However, this was not a randomised study, and as such, there were differences between the groups at baseline in terms of age and spine BMD. Therefore, the prior bisphosphonate group was a higher risk population for fracture, and this may account for the differences in fracture incidence observed. This hypothesis is supported by the fact that the number of vertebral fractures in the prior bisphosphonate group was the same in the first year, during the period of most severe

blunting, as in the second year, when spine BMD increased normally. Furthermore, women were entered into the prior bisphosphonate group if they had either an inadequate response to, or were intolerant of, bisphosphonates. Therefore, we cannot exclude the possibility that selection bias led to women in the prior bisphosphonate group being more resistant to treatment which may also account for the difference in observed fracture incidence.

The reduction in P1NP observed in the bisphosphonate-naïve group in the first year of this study persisted throughout the second year. This observation is in agreement with another study which reported a 14–19% reduction in P1NP in response to strontium ranelate [24]. This is an interesting observation as P1NP is derived from type 1 collagen synthesis [25]. A reduction in the synthesis of type 1 collagen in response to strontium ranelate would not be consistent with the theory that strontium ranelate alters the balance of bone turnover in favour of bone formation resulting in an overall increase in bone tissue [1, 7, 16]. An alternative explanation for the P1NP reduction could be the Adcal D3 tablets as vitamin D has been reported to reduce P1NP in patients with vitamin D levels of less than 30 nmol/l [26]. However, the average vitamin D level in the bisphosphonate-naïve group was over 70 nmol/l, suggesting that it was not a vitamin D-deficient population, and 21 (37.5%) women were already taking calcium/vitamin D supplements prior to study entry. In contrast to our observed reduction in P1NP, Bruyere et al. report that strontium ranelate increases PICP, the C-terminal propeptide of type 1 collagen, by 9.9% [15]. This is more in keeping with the change in bone-specific alkaline phosphatase, a marker of osteoblast activity [25], which is also reported to increase in response to strontium ranelate [1]. Given such mixed results from bone formation markers, it is difficult to draw any conclusions from bone markers regarding whether or not strontium ranelate does have an overall anabolic effect.

There are several limitations to this study. These include inability to randomise the subjects, different bisphosphonate usage prior to study entry and patient selection which have already been discussed with regard to the study [5]. The main limitation with the extension phase was that this was originally planned as a 1-year study, and therefore, subjects had to be enrolled and re-consented into the second year. A number of women chose not to continue into the second year, and this decision may have been influenced by their awareness of their BMD results after the first year. This does not appear to be the case as all but one of the women who decided not to continue into the second year had an increase in their spinal BMD after year 1, and the reasons given for not continuing were: preference for weekly therapy (five women); side effects (two women); and becoming eligible for teriparatide (one woman).

Finally, a different statistic method had to be used in the analysis of the extension phase to account for the missing data due to the number of women who dropped out in the second year. This resulted in one statistical anomaly where the increase in hip BMD at 12 months (0.006 g/cm²) was just statistically significant ($p=0.048$) in the current analysis, whereas in the original study, the same change was not statistically significant ($p=0.096$). No other results were affected by the change in statistical method.

In summary, this study demonstrates that after bisphosphonate exposure, the BMD response to strontium ranelate is blunted for 6 months at the spine after which BMD increases normally. At the hip, a degree of blunting was observed throughout the 2 years of the study, although there was an overall increase in hip BMD in contrast to the heel where no increase in BMD was observed.

Conflicts of interest Servier Laboratories provided the strontium ranelate and a grant to fund the study. ProStrakan provided Adcal D3 as the calcium supplement but no financial support. Servier has paid speaker fees to Dr E Middleton (<£1,000) and Dr M Aye (<£2,000). All authors have no other conflicts of interest. The study design, the data collection, analysis and interpretation, and the manuscript were all carried out by the authors independent of Servier and ProStrakan.

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