

Treatment of Post-menopausal Osteoporosis by Strontium Ranelate in Everyday Practice – DUAL Study

Juraj Payer¹, Peter Vanuga², Zdenko Killinger¹, Sona Tomkova³ and Peter Jackuliak^{1*}

¹Comenius University Faculty of Medicine, 5th Department of Internal Medicine, University Hospital Bratislava, Slovakia

²National Institute of Endocrinology and Diabetology, Lubochna, Slovakia

³Internal Department, Hospital Kosice – Saca, Kosice, Slovakia

Abstract

Introduction: Strontium ranelate (SR) is an effective modality for treatment of postmenopausal osteoporosis. Its effectiveness and acceptability was proven in large phase III trials SOTI and TROPOS and its evaluation in real everyday practice deserves to be more investigated. The objective of the presented study was to evaluate the satisfaction of SR treatment by the patients and to assess the effect of treatment on quality of life and the compliance to SR in every-day practice.

Methods: Study, called DUAL was a one-year prospective open multicentric study performed in rheumatology, endocrinology and orthopedic practices in Slovakia. In total 190 patients were included in 39 centers. Questionnaire concerning satisfaction with treatment, acceptability of treatment, compliance and quality of life was applied at M0, M3, M6 and M12. At M0 and M12 the hip and lumbar spine BMD measurement was performed.

Results: From 190 included patients in total, 85% of them complete the study. Overall satisfaction with treatment as well as with daily intake in form of suspension was around 90% and stable during whole study duration. According to the set of questions regarding the quality of life there is a significant improvement of the overall physical condition and mobility. A strong positive effect on back pain was detected throughout the whole period of study. In 92 patients, BMD at hip level increased by 3.5% ($p \leq 0.05$) whereas in 108 patients, BMD at lumbar spine increased by 6.1% ($p \leq 0.01$). No cardiovascular adverse event was reported.

Conclusions: This study with SR in every-day practice is in accordance with results from phase III trials. The treatment is well accepted and tolerated by patients, leading to a good compliance. Respecting the restriction is the treatment also safe. Efficacy on BMD and benefits on the quality of life, in particular the strong reduction of pain, as soon as after one year could be used as unique opportunities to increase persistence of patients treated with SR to gain full therapeutic effect of the treatment.

Mini-Abstract

The DUAL study evaluated the satisfaction of treatment strontium ranelate by the patients and to assess the effect of treatment on quality of life and the compliance with SR in every-day practice. The study confirms that strontium ranelate is an innovative treatment of postmenopausal osteoporosis.

The authors confirm that all the research meets the ethical guidelines, including adherence to the legal requirements of Slovakia. We assert that there are no conflicts of interest (both personal and institutional) regarding specific financial interests that are relevant to the work conducted or reported in this manuscript.

Keywords: Osteoporosis; Quality of life; Strontium ranelate; Everyday practice; BMD

Introduction

Osteoporosis is considered to be the main cause of fractures among postmenopausal women and as such represents an important health problem [1]. Vertebral and nonvertebral fractures may have a significant impact on the quality of life in patients suffering from osteoporosis [2]. To reduce the risk of fractures, mainly antiresorptive drugs are used in the clinical practice. They are characterized by bone turnover decreasing with decrease both bone formation and bone resorption. On the other hand anabolic agents stimulate bone formation as well as bone resorption and increase the overall bone turnover. Strontium ranelate (SR) is an innovative treatment with a different, so called, dual mode of action on bone turnover, which stimulates bone formation and decreases bone resorption thus rebalancing bone turnover in favor of formation [3].

Strontium ranelate demonstrated a broad antifracture efficacy from the intensive program of phase III studies SOTI [4] and TROPOS [5]. In these trials, SR protects osteoporotic patients from vertebral, non-vertebral and hip fractures. In the SOTI study, a significant vertebral fracture risk reduction of 49% within 1 year and 41% over 3 years

was reported in postmenopausal women. In the TROPOS study, a significant 19% reduction of major nonvertebral fractures was reported under a treatment with SR, and a 36% reduction of hip fractures in women at high risk of hip fractures as well.

The pooled data from these two studies show that a 3-year treatment with SR leads to vertebral anti-fracture efficacy in postmenopausal women independently from baseline osteoporosis risk factors [6]. SR shows efficacy as well as in elderly population (over 80 years of age) [7] as in the youngest post-menopausal women with osteoporosis [8].

***Corresponding author:** Peter Jackuliak, 5th Department of Internal Medicine University Hospital Bratislava Ruzinovska 6, 826 06 Bratislava, Slovakia, Tel: +421 2529 234 80; E-mail: peter.jackuliak@gmail.com

Received: August 07, 2015; **Accepted:** September 10, 2015; **Published:** September 14, 2015

Citation: Payer J, Vanuga P, Killinger Z, Tomkova S, Jackuliak P (2015) Treatment of Post-menopausal Osteoporosis by Strontium Ranelate in Everyday Practice – DUAL Study. Clin Exp Pharmacol 5: 188. doi:10.4172/2161-1459.1000188

Copyright: © 2015 Payer J, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Taking into account all these results, SR is currently the osteoporotic treatment with the best proven efficacy compared to all available treatment [9]. The treatment with SR is linked with improvement of the quality of life and back-pain of treated patients [10]. Overall the medication is well tolerated, and the safety profile is similar to that of the placebo group [4,5].

However, the conditions in large randomized, placebo-controlled studies differ from common real life practice due to strict exclusion criteria for patients, the more stringent follow-up of patients and also the careful investigator selection.

The aim of the presented study was to evaluate the satisfaction to SR treatment by the patients and to assess the effect of treatment on quality of life and the compliance to SR in daily practice within one year.

Subjects and Methods

DUAL study was a one-year prospective open multicentric study performed in 39 rheumatology, endocrinology and orthopedic practices in Slovakia. The primary endpoint was the evaluation of acceptability, tolerability and compliance with strontium ranelate 2g/day. The secondary endpoint was the measurement of BMD changes and the effect on the quality of life as reflect of the efficacy over 1 year. The inclusion criteria were postmenopausal women either naïve osteoporotic patients (T-score less than -2.5SD at vertebral or hip level) or patients having stopped the treatment with antiresorptive treatment (bisphosphonates and/or SERMs) due to intolerance or inadequate treatment effect at least 12 months before inclusion to DUAL study. A treatment with calcium 1000 mg and vitamin D 800 IU per day was recommended.

At inclusion visit (M0) the demographic and medical history data including risk factors were collected. The follow up was done over 12 months with visit at M3, M6 and M12. At each visit the questionnaire divided into four areas: satisfaction to treatment, acceptability of treatment, compliance and quality of life was filled with patient. At M0 and M12 BMD measurement was performed. DXA machine Hologic was used. As this study was not designed to evaluate effect of treatment on fractures, prevalence of osteoporotic fractures at inclusion was obtained only from patient-history and no clinical confirmation was required even during follow-up.

The data collection and standard statistical analyses: t-test for BMD changes and Wilcoxon matched pairs test for quality of life were performed by the sponsor.

Results

In total, 190 patients were included in 39 centers. Mean age was 64.8 years from which 76.7% were newly diagnosed patients. Complete characteristics of the enrolled population are in (Table 1 and 2).

Over 1 year, 8 patients (4.2%) discontinued the treatment. From these patients 7 discontinued at M3 (5 due to GI-intolerance and 2 on own request) and 1 patient at M6 (intolerance GI-intolerance). Additional 21 patients (18.9%) were lost during the follow-up.

At each control visit, the patients were asked questions concerning their satisfaction with the treatment (4 point scale: very satisfied/very good, good, moderate and not at all) and acceptability (4 point scale). The results are summarized in (Table 3 and 4).

Daily intake of SR at bedtime as well the form as suspension was accepted by patients and lead to overall satisfaction with treatment

which was over 93% through whole time period (Table 2). Adverse gastrointestinal events were more frequent at beginning of the treatment, but with low impact on daily life (Table 2). No patient had thromboembolic or cardiovascular adverse event.

Almost 75% of the treated patients would recommend this treatment to their friends.

Only 21% mentioned that they sometimes forgot to take the treatment and almost 84% of the patients took the treatment at recommended at bedtime.

According to the set of questions regarding the quality of life there is a visible trend towards the improvement of the overall physical condition and mobility. A significant effect on back pain was detected throughout the whole period of study. Interestingly, slight increase in worries with osteoporosis was recorded in treated patients (Figure 1). Detailed look on effect of SR treatment on pain over 12 months is summarized in (Table 3).

Only 10% of patients state no pain as a consequence of osteoporosis at inclusion time. After one year of treatment 21.5% (sum of no +0, minor +1, moderate +2, intense +3) of patients report no pain. Treatment with SR leads to improvement of score for 40.53% (sum of positive columns) of patients. Only 6.8% (sum of negative columns) refer worsening of score, what was mainly case of patients with no pain at inclusion. Positive is improvement for patients who suffer from intensive pain at inclusion.

In this study, BMD at hip level increased by 3.5% ($p \leq 0.05$, $n=92$) And BMD at vertebral level increased by 6.1% ($p \leq 0.01$, $n=108$) over 1 year (Figure 2).

Characteristics	Mean \pm SD (n)
Age (years)	64.8 \pm 8,6 (189)
Height (cm)	161 \pm 6.0 (189)
Weight (kg)	66 \pm 10.3 (189)
BMI*	25.6 \pm 3.7 (189)
BMD at lumbar spine (g/cm ²)	0,718 (187)
T-score lumbar spine	-3.0 (187)
BMD at hip (g/cm ²)	0.733 (190)
T-score at hip	-1.9 (190)
Prevalent OP fracture	30.53 % (58)
From which: Vertebral Fx	36.21 % (21)
Peripheral Fx	65.52 % (38)
Family history of osteoporosis	27.9 % (53)
(siblings, grandchildren, aunt, uncle)	
From which among parents	67.9 % (36)
(mother OR father)	
In both parents	3.0 % (1)
(mother AND father)	
Non-smokers	89.4 % (169)
No alcohol consumers	99.5 % (189)
No caffeine consumers	72.1 % (137)
HRT treatment in past	17.2 % (32)
Previous antiresorptive treatment	23.3 % (44: calcitonin 17; alendronate 12; raloxifene 10; risedronate 5)

Plus-minus values are means SD.

*The body-mass index is the weight in kilograms divided by the square of the height in meters.

Table 1: Base-Line Characteristics of the 190 Patients.

Status at M0	Pain changes M0 vs M12						
	-3	-2	-1	0	+1	+2	+3
no (1)	0,00%	0.53%	4.74%	4.74%			
minor (2)		0.00%	1.58%	23.16%	8.95%		
moderate (3)			0.00%	3.68%	17.89%	5.79%	
Intense (4)				0.00%	1.05%	4.74%	2.11%

Table 2: Evolution of pain as a consequence of osteoporosis after 12 months of treatment according to initial status of pain at M0 (score 1= no pain, score 4 = intense pain). Columns with minus refer worsening of score. Columns with plus refer improvement of score. Grid cells indicate impossible changes.

(α) Treatment satisfaction assessment	Answers: very satisfied + good (%)		
	M3	M6	M12
How are you satisfied with the treatment?	93.3	93.7	98.1
How are you satisfied in taking treatment once daily at bedtime?	90.3	87.8	88.4
How do you like to take the drug as a suspension?	89.7	87.3	87.8
(β) Treatment acceptability/tolerability	Answers: not at all + rarely/minor (%)		
	M3	M6	M12
How often did you feel adverse effects of the treatment?	95.0	97.4	98.7
Did these side effects bother you in your daily life?	98.2	94.7	93.0

Table 3: Evaluation of satisfaction with treatment and acceptability at M3, M6 and M12 visits.

Discussion

The success of any osteoporosis treatment strategy depends upon the effectiveness of the therapy and the patient's willingness to adhere to the therapeutic regimen and the tolerability of the treatment. While all OP treatments demonstrated their efficacy in phase III clinical trials, SR has recently been acknowledged as the one of the most efficient [9]. In the SOTI trial, the compliance with SR over 3 years was 83%, while the tolerability was very good [4].

In our study we record a high satisfaction rate to the treatment during the whole duration of the study 93.2% at M3 – 98.1% at M12). When occurring, adverse effects were minor, transient and usually observed within first 3 months of the treatment, confirming thus the observation made during the phase III studies. Interestingly, the occurrence of adverse effects does not bother the patients in their every-day life. In total, only 8 patients discontinued the treatment during the study due to gastrointestinal adverse effects. The study was performed before 2014, when European Medicine Agency (EMA) recommended restriction for use of SR because of cardiovascular adverse event. Nevertheless no cardiovascular or tromboembolic event was detected. We can conclude that treatment with SR is safe, respecting the EMA statement, that SR must not be used in patients with established, current or past history of ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease, or those with uncontrolled hypertension. The treatment of osteoporosis is a chronic treatment, so it is important to motivate the patients to stay on treatment to gain its full benefits [11]. More patients were lost from follow up than discontinued owing to AE, which is more reflected in every-day practice than in the stringent phase III studies and reveals necessity of improvement the close doctor-patient cooperation. The positive motivation of the patients is a key point to increase the persistence of the treatment. Osteoporosis is usually a silent disease. Furthermore, the expected effect of treatments – reduction of fracture risk – is not readily perceptible by the patients.

Then, physicians need alternative attributes to increase motivation of patients. According to the documented significant and fast effect of SR on the improvement of the quality of life [10] and BMD [12] increase, these outcomes could be implemented into the therapeutic strategy to motivate the patients. In our study we confirm the beneficial effect of SR on the quality of life. We record sustainable improvement of overall physical activity and mobility of the treated patients and a decrease of back pain. The active work of physicians with OP explanations during regular visits is visible in the slight increase of worry about osteoporosis among patients in time and reflects in parallel the general perception of OP as a not serious disease among patients population before the inclusion. Therefore patients regularly monitored and educated by physicians should feel more aware about OP even protected by active treatment. Together with these subjective outcomes, the objective BMD increase measurement could be used. In SOTI trial a 5.9% BMD increase in lumbar spine after one-year treatment with SR was observed. Our results with 6.1% increase are in concordance with these findings. To note, this increase is above the reproducibility limit of DXA measurement and thus enables to detect changes of BMD as soon as the first year of treatment. A close correlation (75%) between femoral neck BMD and vertebral fracture risk reduction was previously demonstrated with SR [12] and each 1% femoral neck BMD increase after one year of treatment with SR predicts 3% decrease risk of clinical vertebral fracture over 3 years. The

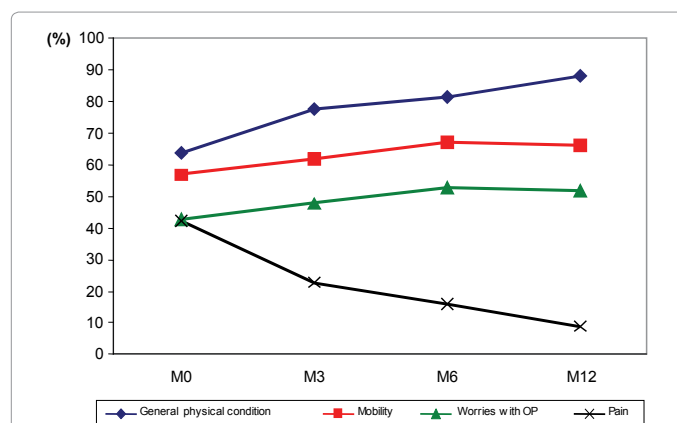


Figure 1: Quality of life: All items were evaluated according to a 4 point scale. For Overall physical condition and Mobility the answers “very good” and “good” were coupled and outlined in the graph. For the Pain and the Worries of OP the answers “intensively” and “moderately” were coupled and outlined in the graph. P-value for each item at M3, M6, M12 vs M0 is < 0,05.

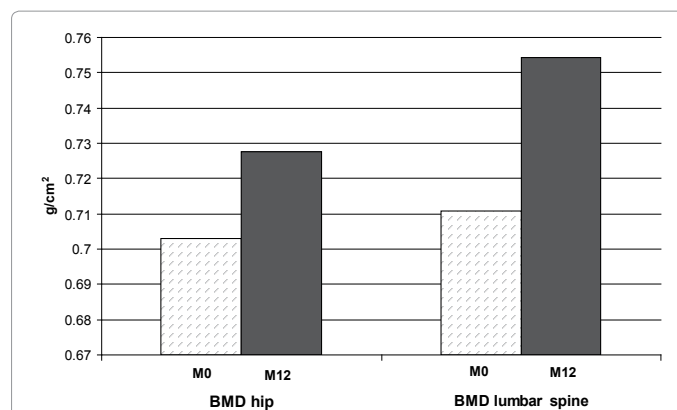


Figure 2: Change of BMD at total hip and vertebral level from M0 to M12.

close link between the increase in BMD and the anti-fracture efficacy of SR could be used as another factor of motivation of patients to persist in the treatment.

There are some limitations of our work. It is an open study, without any comparator and on relatively small number of patients, not powerful enough to detect effect of SR on main outcome of the treatment of OP, i.e. fracture risk reduction. However it is adequate size to detect impact on quality of life improvement.

Conclusion

In conclusion, our study suggests that the effect of treatment with SR in every-day practice is in accordance with the effects of SR phase III trials and the treatment is safe and well accepted and tolerated by the patients. The good tolerability associated with the benefits on quality of life especially efficacy against back pain induced logically a good compliance. These benefits together with significant increase of objective parameter such as BMD can ensure persistence on treatment and adequate osteoporotic fracture risk reduction. In daily use the physicians have to respect the EMA restriction for use is strontium ranelate.

References

1. Ivergard M, Svedbom A, Hernlund E, Compston J, Cooper C, et al. (2013) Epidemiology and Economic Burden of Osteoporosis in Slovakia. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Arch Osteoporos 8: 178-186.
2. Strm O, Borgstrm F, Kanis JA, Compston J, Cooper C, et al. (2011) Osteoporosis: burden, health care provision and opportunities in the EU: a report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Arch Osteoporos 6: 59-155.
3. Marie PJ, Ammann P, Boivin G, Rey C (2001) Mechanisms of action and therapeutic potential of strontium in bone. Calcif Tissue Int 69: 121-129.
4. Meunier PJ, Roux C, Seeman E, Ortolani S, Badurski JE, et al. (2004) The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. N Engl J Med 350: 459-468.
5. Reginster JY, Seeman E, De Vernejoul MC, Adams S, Compston J, et al. (2005) Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: Treatment of Peripheral Osteoporosis (TROPOS) study. J Clin Endocrinol Metab 90: 2816-2822.
6. Roux C, Reginster JY, Fechtenbaum J, Kolta S, Sawicki A, et al. (2006) Vertebral fracture risk reduction with strontium ranelate in women with postmenopausal osteoporosis is independent of baseline risk factors. J Bone Miner Res 21: 536-542.
7. Seeman E, Vellas B, Benhamou C, Aquino JP, Semler J, et al. (2006) Strontium ranelate reduces the risk of vertebral and nonvertebral fractures in women eighty years of age and older. J Bone Miner Res 21: 1113-1120.
8. Devogelaer J, Fechtenbaum J, Kolta S, et al. (2008) Strontium ranelate demonstrates efficacy over 3 and 4 years against vertebral fracture in young postmenopausal women (50-65 years) with severe osteoporosis. Osteoporos Int 19: S14-S15.
9. Kanis JA, Burlet N, Cooper C, Delmas PD, Reginster JY, et al. (2008) European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int 19: 399-428.
10. Marquis P, Roux C, de la Loge C, Diaz-Curiel M, Cormier C, et al. (2008) Strontium ranelate prevents quality of life impairment in post-menopausal women with established vertebral osteoporosis. Osteoporos Int 19: 503-510.
11. Payer J, Killinger Z, Ivana Sulkov, Celec P (2007) Therapeutic adherence to bisphosphonates. Biomed Pharmacother 61: 191-193.
12. Bruyere O, Roux C, Detilleux J, Slosman DO, Spector TD, et al. (2007) Relationship between bone mineral density changes and fracture risk reduction in patients treated with strontium ranelate. J Clin Endocrinol Metab 92: 3076-3081.