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Original article

Clinically meaningful effect of strontium ranelate on symptoms in knee osteoarthritis: a responder analysis

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Abstract

Objectives. The aim of this study was to assess the efficacy of strontium ranelate in improving symptoms in knee OA.

Methods. Symptoms were assessed over 3 years in patients with primary knee OA receiving strontium ranelate 2 g/day ($n = 454$), 1 g/day ($n = 445$) or placebo ($n = 472$) in the Strontium Ranelate Efficacy in Knee Osteoarthritis Trial. Clinical response was evaluated using WOMAC subscores, minimal perceptible clinical improvement (MPCI), minimal clinically important improvement (MCII) and a modified OMERACT–Osteoarthritis Research Society International (OARSI) responder definition. Patients who withdrew prematurely from the study were considered non-responders.

Results. There was no significant effect on symptoms for strontium ranelate 1 g/day. At the dosage of 2 g/day, strontium ranelate was associated with greater response than placebo in terms of $\geqslant$20% improvement in WOMAC pain from baseline to the last visit (58% *vs* 47%, $P = 0.002$) and $\geqslant$50% improvement in WOMAC pain (42% *vs* 36%, $P = 0.083$). Significant differences were found in MPCI response for WOMAC pain (52% *vs* 40%, $P < 0.001$), stiffness (47% *vs* 39%, $P = 0.009$) and physical function (46% *vs* 37%, $P = 0.009$) and in MCII response for WOMAC physical function (46% *vs* 37%, $P = 0.013$). There were also more OMERACT-OARSI-like responders with strontium ranelate (44% *vs* 35%, $P = 0.004$). The treatment–placebo difference in MPCI response for WOMAC pain was significant after 6 months ($P = 0.024$), while that in MPCI and MCII response for WOMAC physical function reached significance after 12 months ($P = 0.027$ and $P = 0.019$, respectively).

Conclusion. Treatment with strontium ranelate 2 g/day over 3 years is associated with a clinically meaningful improvement in pain from 6 months as well as physical function and stiffness as assessed by the number of responders above thresholds of clinical relevance.

Trial registration: Current Controlled Trials. http://www.controlled-trials.com/ (ISRCTN41323372).

Key words: osteoarthritis, pain, responder criteria, SEKOIA, strontium ranelate, symptoms.

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Introduction

OA is associated with a variety of symptoms, including pain, stiffness and loss of physical function [1]. Osteoarthritic pain is intermittent and is greater during or after physical activity, while stiffness generally occurs after periods of physical inactivity, such as in the morning. Inflammatory flares can exacerbate symptoms over the course of the disease. Osteoarthritic symptoms lead to a progressive loss of physical function, with patients reporting limitations on daily activities such as walking or climbing stairs.

CLINICAL SCIENCE

Subjective symptoms like pain and stiffness are notoriously difficult to quantify and can be affected by many other conditions. In clinical research, symptomatic improvement in OA is usually reported for patient populations via analysis of mean changes in continuous variables, e.g. the WOMAC scale [2] or a visual analogue scale (VAS). While this provides a measure of the magnitude of variation of group effects, it does not usually translate into an understanding of the degree of improvement experienced by individual patients [3]. The interpretation of these measures in terms of a clinically meaningful improvement for patients has proved fundamental to the development of treatments aimed at improving the symptoms of OA. Several responder criteria have been developed to categorize individual response to treatment within the setting of randomized clinical trials. These include response on the WOMAC scale [4], as well as a set of responder criteria developed by the OMERACT–Osteoarthritis Research Society International (OMERACT-OARSI), which identifies responders on the basis of improvement in both knee pain and physical function [5]. Other thresholds have been developed to determine the point at which patients consider that there is a minimal perceptible clinical improvement (MPCI) [6] or a minimal clinically important improvement (MCII) [7].

The Strontium Ranelate Efficacy in Knee Osteoarthritis Trial (SEKOIA) explored the effect of 3 years of treatment with strontium ranelate 1 and 2 g/day *vs* placebo in patients with primary knee OA [8]. The main analysis of SEKOIA showed that treatment with both dosages of strontium ranelate produced a significant decrease in joint space narrowing (reduction in structural progression) *vs* placebo ($P = 0.018$ at 2 g/day and $P < 0.001$ at 1 g/day). The effect on structure was accompanied by a beneficial effect on symptoms at 2 g/day in terms of the change from baseline to the last visit (last observation carried forward) on the total WOMAC score ($P = 0.045$) and WOMAC pain subscore ($P = 0.028$) [8]. The dosage of 1 g/day had no effect on symptoms ($P = 0.75$ and $P = 0.97$, respectively) [8]; the dosage of 2 g/day is therefore expected to be the most appropriate for clinical practice. The aim of this article is to describe the clinical effect of strontium ranelate *vs* placebo on a range of responder criteria for symptoms in the SEKOIA trial.

Methods

Study design

SEKOIA was a 3-year randomized, double-blind, placebo-controlled, phase 3 trial carried out in 98 centres in 18 countries. The SEKOIA trial is a registered trial (ISRCTN41323372). Local ethical approval was obtained for SEKOIA in the countries concerned and all patients gave written informed consent. Eligible patients were age $\geqslant 50$ years with symptomatic knee OA according to ACR criteria [9] [knee pain $\geqslant 40$ mm on a 100-mm VAS on more than half of the days of the previous month, Kellgren–Lawrence grade 2 or 3 and joint space width (JSW) 2.5–5 mm]. At inclusion in the main study, patients were randomly allocated to strontium ranelate 1 g/day, 2 g/day or placebo (one sachet daily with water at bedtime at least 2 h after food) by balanced randomization with stratification by centre and by gender [8]. Patients and investigators were blinded to treatment allocation and study treatments were identical in appearance. During the study period, patients were allowed pain relief if required, although any pain medication was stopped at least five half-lives before symptom assessment, which corresponds to about 48 h in most cases (72 h for celecoxib) [8]. Treatments affecting cartilage (chondroitin, glucosamine sulphate $\geqslant 1500$ mg) or bone metabolism (bisphosphonates) were not permitted, and corticosteroids were allowed only in case of severe knee flare or medical requirement (oral, inhaled >1500 μg/day or IA). Further details of the study design and the main results are published elsewhere [8, 10].

Symptoms of knee OA were assessed every 6 months using the WOMAC Index, a 24-item condition-specific questionnaire that evaluates OA health status in terms of a total score and three subscores for pain, stiffness and physical function, with lower scores indicating better status [2]. Quality of life was assessed every 6 months using the 36-item Short Form Health Survey (SF-36), a generic 36-item health questionnaire, with a 1-month recall. The SF-36 responses obtained were aggregated into a physical component summary score and a mental component summary score.

Responder analyses

Responder analyses compared patients receiving strontium ranelate 1 g/day, 2 g/day and placebo. Response to treatment was evaluated as a percentage improvement between baseline and the last available value of $\geqslant 20\%$ or $\geqslant 50\%$ in WOMAC pain, physical function and stiffness subscores [4]. MPCI responders for pain, physical function and stiffness were defined as patients with a mean change of -9.7, -9.3 and -10.0 mm from baseline to the last available visit in WOMAC pain, physical function and stiffness subscores, respectively, on the basis of previous reports [6]. MCII responders for WOMAC physical function were defined as patients with a change from baseline to the last available visit of $\geqslant -9.1$ mm [7].

Response using the exact OMERACT-OARSI criteria [5] could not be directly evaluated since patient global assessment was not recorded during the trial. For the purposes of our analysis, we therefore employed a modified OMERACT-OARSI responder definition, without patient global assessment. Thus, in our study, OMERACT-OARSI responders were considered as patients with either (i) $\geqslant 50\%$ improvement and an absolute change of at least 20 mm in the WOMAC pain or function subscores, or (ii) $\geqslant 20\%$ improvement and an absolute change of at least 10 mm in the WOMAC pain subscore as well as $\geqslant 20\%$ improvement and an absolute change of at least 10 mm in the WOMAC function subscore. Exclusion of the patient global assessment may slightly underestimate the number of OMERACT-OARSI responders in our study.

MPCI response and quality of life

In order to evaluate the link between response and quality of life, the population was divided according to whether they were MPCI responders or non-responders on the WOMAC physical function scale (independent of treatment allocation at baseline). The changes in quality of life on the SF-36 physical and mental component summary scores were compared between the two groups (responders and non-responders). The same analysis was also performed on responders with $\geqslant$20% improvement in the WOMAC pain subscore as well as on MCII responders for the WOMAC physical function subscore.

Statistical methods

Baseline characteristics are presented as descriptive statistics in the intention-to-treat (ITT) population of the overall SEKOIA study, which included all randomized patients who had taken at least one dose of study treatment and who had an assessable baseline and one post-baseline radiographic evaluation of JSW [8]. All responder analyses described herein were *post hoc*, and the main analysis was carried out in the ITT population by considering patients who withdrew prematurely from the study (for whatever reason) as non-responders. In addition to this conservative approach, the analysis was also performed in the global ITT population (without taking into account withdrawn patients as non-responders) as well as in the randomized population. Estimates (E) of the difference [standard error (S.E.)] between groups in terms of the percentage of patients reaching the various thresholds of clinical relevance for the different WOMAC subscores are provided with 95% CIs and the corresponding *P*-values (from a chi-squared test). Differences in the SF-36 summary scores between responders and non-responders were compared using a general linear model with baseline as the covariate and gender and centre as fixed factors, to produce estimates (S.E.) and corresponding 95% CIs and *P*-values. The two-sided type 1 error rate was fixed at 0.05. No adjustment for type 1 error was performed since the analyses on these secondary endpoints were considered as supportive. Statistical analyses were initially performed by the first author (O.B.) and subsequently by the Biostatistics Division of the Institut de Recherches Internationales Servier (IRIS) using SAS software (versions 9.1 and 9.2; SAS Institute, Cary, NC, USA).

Results

Effect of strontium ranelate on responder criteria

The baseline characteristics of the randomized and ITT populations have been described elsewhere [8], and there were no relevant between-group differences. Briefly, in the randomized population (strontium ranelate 1 g/day, 558 patients; 2 g/day, 566 patients; placebo, 559 patients), there was a majority of women (70%), mean age was 62.9 years (S.D. 7.5) and BMI was 29.9 kg/m^2 (S.D. 5.0). They had documented knee OA in terms of JSW [mean 3.50 mm (S.D. 0.84)], Kellgren–Lawrence grade (62% in grade 2, 38% in grade 3) and WOMAC total score [mean 132.4 mm (S.D. 62.4)]. About three-quarters (76%) of patients received at least one symptomatic treatment for OA during the study (25% propionic acid derivatives, 18% acetic acid derivatives and 39% anilides), 46% took analgesics with an indication in OA, 5% took systemic corticosteroids, 11% took opioids and 8% took cyclooxygenase-2 (COX-2) inhibitors (e.g. celecoxib and lumiracoxib). The ITT population included 445 patients on strontium ranelate 1 g/day, 454 patients on strontium ranelate 2 g/day and 472 patients on placebo. The annualized dropout rate during the main study was 14%, mainly for non-medical reasons [8]. The patients were followed for a mean of 30 months and mean compliance was 93%.

There was no significant effect on any of the responder criteria analysed for strontium ranelate 1 g/day *vs* placebo, including the WOMAC subscores, MPCI, MCII and OARSI-OMERACT criteria with similar response rates between the two treatment groups (data not shown).

The results for the analyses of the effect of strontium ranelate 2 g/day on the responder criteria are presented in Table 1. In the ITT population with withdrawn patients as non-responders, treatment with strontium ranelate 2 g/day was associated with significantly greater response rates than placebo measured in terms of $\geqslant$20% improvement in WOMAC pain from baseline to the last available visit (58% *vs* 47%, $P = 0.002$) and a greater response rate measured in terms of $\geqslant$50% improvement in WOMAC pain (42% *vs* 36%, $P = 0.083$) (Table 1). Analysis of response in terms of MPCI and MCII also showed a better response to strontium ranelate 2 g/day than placebo (Table 1) [6]. The difference in MPCI response *vs* placebo was significant for all three WOMAC subscores—pain (52% responders for strontium ranelate *vs* 40% for placebo, $P < 0.001$), stiffness (47% *vs* 39%, $P = 0.009$) and physical function (46% *vs* 37%, $P = 0.009$)—as was MCII response for the WOMAC physical function subscore (46% *vs* 37%, $P = 0.013$). There were significantly more OMERACT-OARSI responders with strontium ranelate 2 g/day than placebo (44% *vs* 35%, $P = 0.004$). The relative odds of having a clinically relevant improvement of osteoarthritic symptoms assessed via the various responder criteria in Table 1 is increased by up to 30% when the patients were treated by strontium ranelate 2 g/day *vs* placebo.

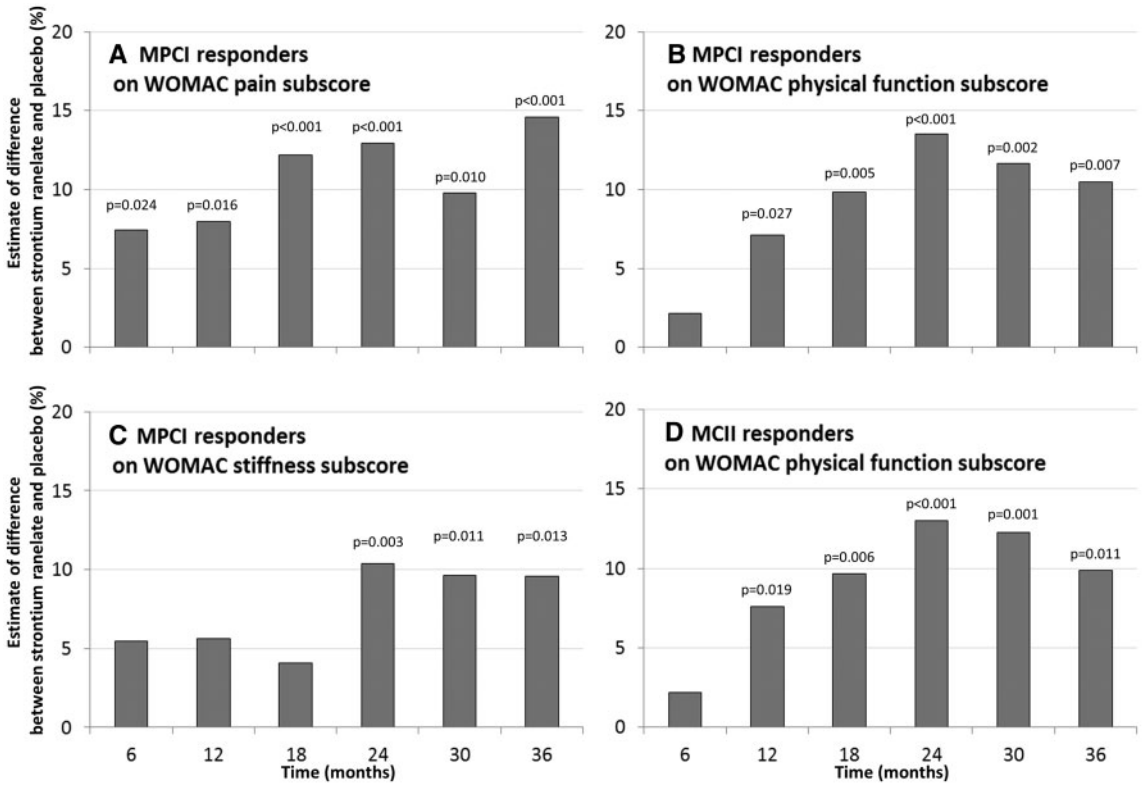
The above results were similar to those found in the ITT population that did not take into account the effect of withdrawals (Table 1), with significant strontium ranelate–placebo differences for MPCI responders on the WOMAC subscores for pain ($P = 0.001$), stiffness ($P = 0.025$) and physical function ($P = 0.008$) and for MCII responders on the WOMAC physical function subscore ($P = 0.012$). There were also significant differences for $\geqslant$20% improvement in the WOMAC pain ($P = 0.01$) and OMERACT-OARSI-like responders ($P = 0.035$) and a trend for $\geqslant$50% improvement in WOMAC pain ($P = 0.078$) (Table 1). Analysis of the responder criteria was also performed in the randomized population and gave similar results for MCII WOMAC physical function ($P = 0.021$) and MPCI WOMAC pain ($P = 0.005$), physical function ($P = 0.015$) and stiffness ($P = 0.054$).

Table 1 Comparison of response between the strontium ranelate and placebo groups based on WOMAC subscores

	ITT population					ITT population (withdrawn patients considered as non-responders)				
	Patients above threshold, *n* (%)					Patients above threshold, *n* (%)				
	Placebo	Strontium ranelate 2 g/day	Difference *vs* placebo, E (s.e.) (95% CI)	*P*-value	RR (%)	Placebo	Strontium ranelate 2 g/day	Difference *vs* placebo, E (s.e.) (95% CI)	*P*-value	RR (%)
Responders in terms of improvement of symptoms										
WOMAC pain										
⩾20% improvement	297 (64)	317 (72)	8.04 (3.09) (1.98, 14.09)	0.010	12.5	219 (47)	253 (58)	10.30 (3.31) (3.82, 16.78)	0.002	23.4
⩾50% improvement	208 (45)	223 (51)	5.85 (3.32) (−0.65, 12.36)	0.078	13.3	169 (36)	185 (42)	5.62 (3.24) (−0.74, 11.98)	0.083	16.7
WOMAC stiffness										
⩾20% improvement	280 (60)	289 (65)	4.61 (3.21) (−1.67, 10.90)	0.15	8.3	208 (45)	232 (52)	7.50 (3.30) (1.03, 13.97)	0.024	15.6
⩾50% improvement	205 (44)	210 (47)	3.02 (3.31) (−3.46, 9.50)	0.36	6.8	157 (34)	177 (40)	6.08 (3.19) (−0.17, 12.34)	0.057	17.6
WOMAC physical function										
⩾20% improvement	262 (56)	282 (64)	7.31 (3.24) (0.96, 13.67)	0.025	14.3	202 (43)	223 (50)	6.78 (3.30) (0.31, 13.26)	0.040	16.3
⩾50% improvement	181 (39)	176 (40)	0.80 (3.24) (−5.55, 7.16)	0.80	2.6	142 (31)	145 (33)	2.12 (3.08) (−3.93, 8.17)	0.49	6.5
Modified OMERACT-OARSI	221 (47)	244 (54)	6.96 (3.29) (0.52, 13.40)	0.035	14.9	165 (35)	201 (44)	9.32 (3.20) (3.04, 15.59)	0.004	25.7
MPCI responders										
WOMAC pain	255 (55)	289 (66)	10.58 (3.23) (4.24, 16.91)	0.001	20.0	185 (40)	231 (52)	12.51 (3.29) (6.06, 18.96)	<0.001	30.0
WOMAC stiffness	247 (53)	270 (60)	7.36 (3.27) (0.96, 13.76)	0.025	13.2	181 (39)	212 (47)	8.54 (3.26) (2.15, 14.93)	0.009	20.5
WOMAC physical function	229 (49)	257 (58)	8.74 (3.29) (2.28, 15.20)	0.008	18.4	172 (37)	202 (46)	8.59 (3.25) (2.21, 14.96)	0.009	24.3
MCII responders										
WOMAC physical function	231 (50)	257 (58)	8.31 (3.29) (1.85, 14.77)	0.012	16.0	174 (37)	202 (46)	8.16 (3.26) (1.77, 14.54)	0.013	24.3

Responders to treatment with strontium ranelate 2 g/day and placebo in terms of improvement of symptoms, MPCI and MCII. *P*-value for treatment *vs* placebo (chi-squared test). E (s.e.) of between-group difference of percentage of patients reaching thresholds of clinical relevance. Number of patients with available data: WOMAC pain subscore: 441 strontium ranelate (2 g/day), 464 placebo; WOMAC stiffness subscore: 449 strontium ranelate (2 g/day), 468 placebo; WOMAC physical function subscore: 444 strontium ranelate (2 g/day), 466 placebo; modified OMERACT-OARSI criteria: 452 strontium ranelate (2 g/day), 470 placebo. ITT: intention to treat; MPCI: minimal perceptible clinical improvement; MCII: minimal clinically important improvement; E: estimate; s.e.: standard error; OARSI: Osteoarthritis Research Society International; RR: relative risk.

FIG. 1 Differences in response to treatment between patients on strontium ranelate 2 g/day and placebo



Responders to treatment with strontium ranelate 2 g/day and placebo from baseline to the last available visit in terms of the percentage of patients with improvement above the thresholds for MPCI on (**A**) the WOMAC pain subscore, (**B**) the WOMAC physical function subscore, (**C**) the WOMAC stiffness subscore and (**D**) MCII on WOMAC physical function over the course of the study. Withdrawn patients are considered as non-responders. *P*-value for treatment *vs* placebo (chi-squared test). MPCI: minimal perceptible clinical improvement; MCII: minimal clinically important improvement.

The treatment–placebo difference in percentage of responders in terms of MPCI and MCII in the strontium ranelate 2 g/day and placebo groups over the 3 years of the trial are presented in Fig. 1. The treatment–placebo difference in MPCI responders reached significance after 6 months for the WOMAC pain subscore ($P = 0.024$) (Fig. 1A) and after 12 months for WOMAC physical function ($P = 0.027$) (Fig. 1B), and remained as such until the end of the 3-year study period. The strontium ranelate–placebo difference in the rate of MPCI responders on the WOMAC stiffness subscore was significant from 24 months ($P = 0.003$) (Fig. 1C). The treatment–placebo difference in the rate of MCII responders was significant after 12 months ($P = 0.019$) (Fig. 1D).

MPCI response and quality of life

The SEKOIA population was divided into 526 MPCI responders and 771 MPCI non-responders on the WOMAC physical function subscore independent of treatment allocation. The MPCI responders had a net increase in the SF-36 physical component summary score [mean +0.82 (S.D. 1.31)] *vs* no change for the MPCI non-responders [0.03 (1.18)] with a significant between-group difference [E 0.75 (S.E. 0.07), 95% CI 0.62, 0.88, $P < 0.001$]. Similar results were found for the mental component summary score with an increase for MPCI responders [mean 0.22 (S.D. 1.51)] *vs* a decrease for MPCI non-responders [−0.22 (1.51)] [E 0.41 (S.E. 0.08), 95% CI 0.26, 0.56, $P < 0.001$] and for all dimensions of the SF-36 (data not shown). Results were similar when comparing responders and non-responders for 20% and 50% improvement in the WOMAC pain, stiffness and physical function subscores, as well as for MPCI pain and stiffness subscores and MCII.

Discussion

Treatment with strontium ranelate 2 g/day *vs* placebo led to a significantly higher proportion of patients reaching recognized clinically relevant boundaries for symptomatic response to treatment on the WOMAC scale in terms of MPCI and MCII and using modified OMERACT-OARSI criteria [5]. Nearly three-fifths (58%) of treated patients reported an improvement of $\geqslant$20% on the WOMAC pain subscore (23% increase in response relative to placebo, $P = 0.002$) and nearly half (44%) responded according to the modified OMERACT-OARSI criteria (26% increase in response relative to placebo, $P = 0.004$).

Similar proportions of patients on strontium ranelate 2 g/day fulfilled the criteria for MPCI for WOMAC pain (52%) or MCII for WOMAC physical function (46%) [30% ($P < 0.001$) and 24% ($P = 0.013$) increases in response relative to placebo, respectively]. Treatment–placebo differences in rates of response reached significance after 6–24 months, notably with a significant difference in MPCI responders for WOMAC pain at 6 months ($P = 0.024$). Beyond 24 months of treatment, the rates of clinical response either continued to increase or were stabilized with time, depending on the criterion studied.

The robustness of these findings is demonstrated by the consistency of the results for strontium ranelate 2 g/day across the various response criteria. These results were found using a conservative analysis in which patients who withdrew prematurely (for whatever reason) were considered as non-responders. Similar results were observed in the randomized set, which reinforces our conclusions. The effect also appears to correlate with a better health status as measured by an internationally recognized quality of life questionnaire (SF-36).

Responder criteria are important in knee OA insofar as they measure a clinically meaningful change for the patient. The MCII results for strontium ranelate 2 g/day are particularly relevant to patients since they represent the number of patients with an improvement that they perceive as important, i.e. a treatment target from a patient's perspective. For this reason, this item is recommended as a secondary endpoint by the European Medicines Agency for drugs developed as symptom modifying in OA [11]. Such responder criteria have been reported to be affected by the severity of symptoms at baseline, but not by age, disease duration or gender [7]. When the MCII analyses for strontium ranelate 2 g/day were performed taking into account baseline severity (separation by tertiles), the results for strontium ranelate 2 g/day were significant (MCII responders on the WOMAC physical function subscore, $P = 0.026$).

Our results for strontium ranelate 2 g/day on the WOMAC scale indicate the presence of a substantial response to placebo in the SEKOIA trial, particularly at the first (6-month) visit. Like other chronic diseases involving pain, observation of a strong placebo effect for pain and function is not unusual in studies in OA [12–14]. A longitudinal study in patients with knee OA or at high risk of developing the condition estimated that between 24% and 39% of patients may reach thresholds for MCII for WOMAC physical function within 30 months [15]. While there was no information in that study regarding any impact of treatment on symptoms, only 39% had previously received some form of OA medication.

Pain in OA is most likely linked to inflammation and a parallel impact on bone [1]. In view of the results of preclinical studies [16–18], one might suppose that the mechanism of action of strontium ranelate 2 g/day occurs via the subchrondal bone. In this context, a previous *post hoc* study of patients with osteoporosis and radiological spinal OA reported a significant reduction in back pain after 3 years of treatment with strontium ranelate 2 g/day [19]. Other possible mechanisms are currently being investigated.

Concomitant use of pain medication was authorized during the study, since it would have been unethical to forbid them. The use of concomitant treatments was balanced between the treatment and placebo groups throughout the SEKOIA study. To avoid any impact on symptoms and pain evaluation, patients were requested to stop their pain medication sufficiently early prior to a visit to allow for complete washout of pain medication [8]. Detailed instructions were given to investigators and procedures were set up to follow up on this point to ensure that the instructions were carried out.

There are limitations to the analysis presented here. First, it is a *post hoc* analysis. However, the consistency of our observations, in terms of response measured by a variety of criteria, indicates the robustness of our conclusions. Second, the dropout rate in the SEKOIA trial was relatively high (14% annualized), although it was similar to other trials in the field [8]. This contributed to the large number of missing data in our analysis, which may be considered as a limiting factor. However, to handle these missing data, a conservative approach was adopted, i.e. patients who withdrew prematurely from the study (for whatever reason) were considered as non-responders. Third, pain is a subjective experience with a large number of confounding factors (psychological status, co-morbidities, medication, cultural context, etc.). It is measured using patient-reported outcomes, which have a number of associated biases and can be difficult to interpret. In SEKOIA, we evaluated pain using the WOMAC scale, which has acceptable validity, reliability, responsiveness and relative efficiency in knee OA [2]. Moreover, the SEKOIA protocol homogenized the evaluation of pain within the study via standardized written instructions for the patients, which were similar in all countries and could be completed without help from the investigator; patient questionnaires were filled out before the visits to avoid any investigator bias.

In conclusion, treatment with strontium ranelate 2 g/day over 3 years is associated with a beneficial effect on symptoms, as demonstrated by a greater number of patients with an MCPI or MCII or who were considered to be responders according to a modified OMERACT-OARSI definition. Our results are further supported by the greater number of patients with a 20% improvement in symptoms. This effect is significant from 6 months onwards, depending on treatment and the criterion considered. This improvement in the symptoms of OA can be expected to translate into better health status in terms of quality of life.

Rheumatology key messages

- Clinically relevant improvement in OA symptoms was greater with strontium ranelate 2 g/day than with placebo.
- Improvement of OA symptoms with strontium ranelate 2 g/day could enhance patients' quality of life.

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