

## NEWS

### Strontium Ranelate: A New Tune, or Just More Heavy Metal?

*Supporters of the agent emphasize a unique mechanism of action, but top experts remain skeptical*

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A drug that not only inhibits bone resorption, but also stimulates new bone formation – this is often described as the holy grail of osteoporosis treatment. Strontium ranelate, an agent developed by the French pharmaceutical company Servier and available in scores of countries throughout the world, is marketed by the company as the first osteoporosis drug to achieve this goal. The experts who have investigated the workings of the medication in the most detail also highlight a unique dual mechanism of action. Though they are careful to note that the changes induced by the drug at the cellular level are modest compared to other osteoporosis treatments like bisphosphonates and PTH, they nonetheless emphasize strontium ranelate's simultaneous bone-building and anti-resorptive effects.

However, while there is little debate in the bone field about the anti-fracture efficacy of strontium ranelate, which has been demonstrated in two phase 3 clinical trials, virtually all of the top osteoporosis experts who spoke to *BoneKEy* emphasize that precisely how the drug exerts its anti-fracture effect in people remains, to a very large degree, uncertain. "While strontium ranelate has been shown to reduce fracture risk and appears to have low toxicity, we do not yet understand exactly how it works. Determining the mechanism(s) of action will be critical to fully evaluating its role in therapy," says Lawrence Raisz, the director of the University of Connecticut Center for Osteoporosis who has investigated strontium ranelate's molecular mechanism of action. Furthermore, most of the outside experts interviewed for this article are skeptical in particular about the dual mechanism of action theory. While future

research findings may prove otherwise, they say that the existing scientific evidence simply isn't yet strong enough to support the contention that strontium ranelate prevents fractures primarily through a novel effect on bone remodeling.

#### **The Development of Strontium Ranelate**

Experiments initiated in the 1980s found that strontium chloride, when administered to intact rats and mice, produced modest increases in bone formation, as well as modest decreases in bone resorption. Building upon this early work, experiments in the 1990s with the distrontium salt strontium ranelate also showed that the drug resulted in mild decreases in resorption, and in the maintenance of bone formation, in ovariectomized rats. "This was the beginning of the story," says Pierre Marie, who pioneered these early investigations and is now a director of research at INSERM in Paris. Since this initial work, Dr. Marie says, the tale has continued to unfold: strontium ranelate has been tested in other animal models and in clinical trials. In the two phase 3 clinical trials of the medication, the 2004 SOTI study found a 41 to 49% reduction in vertebral fracture risk, while the 2005 TROPOS study found a 16% reduction in risk for all non-vertebral fractures.

Some of the most convincing evidence to support the dual mechanism of strontium's action in bone, says Dr. Marie, who serves as a consultant for Servier and has received research funding from the company in the past, comes from the three-dimensional analysis of bone micro-architecture characteristic of animals and people treated with the drug. For instance, he notes that intact rats treated with the agent exhibit

increases in vertebral trabecular thickness and decreases in trabecular separation, compared to untreated animals. Micro-CT analysis of iliac crest bone biopsies taken from the clinical trial participants reveals similar changes in patients treated with the drug, compared to placebo subjects. Complementing this research, Dr. Marie further notes, are data *in vitro* from several labs showing that strontium ranelate inhibits osteoclast activity and promotes osteoblast replication. Finally, Dr. Marie points out that the clinical trials have also shown increases in markers of bone formation, and decreases of markers of bone resorption, of about 10%.

Those who believe that strontium ranelate has a unique dual mechanism of action are quite careful to note that the changes in bone remodeling induced by strontium ranelate are modest, particularly in comparison to bisphosphonates, which produce a much greater inhibition of bone resorption, and to PTH, which produces a much greater increase in bone formation. With this caveat in mind, though, and when considering all of the studies together, including findings *in vitro*, *in vivo*, and from the clinical trials, "the data indicate that strontium ranelate acts differently on the two steps of bone metabolism by dissociating bone resorption and formation," Dr. Marie concludes, as do many other proponents of the drug.

### **What Explains the Anti-Fracture Effect in Humans?**

Despite the optimism of the drug's supporters, there is widespread skepticism in the bone field that strontium ranelate's effectiveness at preventing fractures in humans results from a unique dual effect on bone resorption and formation. The primary objection to the hypothesis concerns the nature and quality of the existing evidence: most of the data, the skeptics say, come from studies *in vitro* and from animal investigations whose relevance to what actually happens in humans taking the medication is unclear.

Furthermore, many of the key findings from human studies are unconvincing to them.

"The changes were so small both in the parameters of bone formation and of bone resorption," says Socrates Papapoulos, a professor of medicine at Leiden University Medical Center. "The dual mechanism of action hypothesis could be right, but not based on these data." Because the absolute changes in markers found in the clinical trials are modest, most experts say the most generous conclusion the existing data allow is that strontium ranelate mildly inhibits resorption and, perhaps, *maintains* bone formation. But whether resorption and formation actually move in opposite directions – whether new bone is formed – is the crux of the issue, and skeptics are not yet convinced.

The evidence from human studies often cited for a bone-building effect of strontium ranelate comes from the bone biopsies taken from clinical trial patients, but critics stress that these biopsies were unpaired – the studies compared biopsies from subjects receiving strontium ranelate to biopsies from those receiving placebo, and thus offer only a limited, cross-sectional view of the issue. A comparison of biopsies obtained at baseline, before treatment, to biopsies obtained after treatment would be far more persuasive, they say.

An additional limitation related to the biopsy findings, made available at the 2005 and 2006 ASBMR meetings, is that, to date, they have not been published, thus making a full analysis and consideration of the data unavailable to the field. "There is some micro-CT analysis suggesting that with strontium ranelate treatment the trabeculae become more plate-like, and that bone volume and cortical thickness may increase, but we must view these results with caution since they have only been presented in abstract form," says Ghada El-Hajj Fuleihan, a professor of medicine and director of the Calcium Metabolism and Osteoporosis Program at the American University of Beirut Medical Center who penned the editorial that accompanied the publication of the SOTI study in the *New England Journal of Medicine* in early 2004.

## One Alternative Hypothesis

If strontium ranelate does not prevent fractures through a simultaneous anti-resorptive and pro-anabolic effect, how else might it work? One potential explanation that reflects many of the issues problematic to skeptics of the drug is that the mere presence of strontium in bone may be the major factor underlying its anti-fracture activity.

"What is very clear is that strontium is deposited into bone crystals as a heavy element, and so the mechanism of fracture reduction or improving bone strength could simply be by deposition of the element within bone," says Michael McClung, director of the Oregon Osteoporosis Center. "One does not have to invoke specific changes in bone remodeling to account for its effectiveness." Dr. McClung's interpretation of the evidence is that the effect of strontium ranelate on bone remodeling is modest, and that the possibility exists that strontium's effect is primarily due to changes in mechanical properties rather than to a unique alteration in bone remodeling. All of the drug's skeptics acknowledge the possibility raised by Dr. McClung, though they stress there is no experimental evidence yet to support it.

Those who speak in support of strontium's dual effect on bone remodeling are aware of these objections and point to specific studies to refute them. For instance, one argument they make is that animal studies show no correlation between the increase of bone biomechanical resistance seen with strontium ranelate treatment and the level of bone strontium content. Since the evidence shows no link between the strength of the bone and the level of strontium present in the bone, strontium makes bone stronger because it alters bone cell activity in favor of formation, according to this line of thinking.

Another argument by the drug's supporters is that only a small amount of strontium is ionically substituted for calcium into hydroxyapatite crystals, and these crystals exhibit no abnormalities. Furthermore, strontium ranelate treatment does not adversely affect bone mineralization. "We

have never observed a significant modification, an increase or a decrease, of the degree of mineralization, that is, of the density at the tissue level," says Georges Boivin, a director of research at INSERM who has published findings from monkeys on this subject. Dr. Boivin, who has received research funding from Servier, attributes the increase in bone mineral density (BMD) seen with strontium ranelate treatment mainly to beneficial changes in bone mass or micro-architecture.

A third line of reasoning contends that the small proportion of strontium that replaces calcium in bone crystals cannot completely account for the changes in BMD observed with strontium ranelate treatment. This is true even when those BMD changes are corrected for the fact that strontium, as a heavier element with a higher atomic number than calcium, will artifactually increase BMD. A recent study documenting an association between changes in BMD and changes in fracture risk seen with the administration of strontium ranelate further weakens the argument that the mere deposition of strontium in bone is the key phenomenon, according to Jean-Yves Reginster, senior author of the study. "When you see this very strong relationship between the increase in BMD and the decrease in fracture risk, it is clear that the presence of strontium in bone only plays a trivial role in the reduction of fractures," says Dr. Reginster, a co-author of the clinical trial studies and a professor of epidemiology, public health and health economics at the University of Liège in Belgium. Dr. Reginster also consults for Servier.

However, as with most aspects of strontium ranelate's effects on bone, there is great uncertainty regarding how much of the BMD change is attributable simply to strontium's presence in bone

"How much of the effect is due to the physical presence of strontium? I honestly don't think we know," says Glen Blake, a medical physicist at King's College London Medical School who has studied this issue. Based on his studies, Dr. Blake estimates that at least 80% of the change in BMD observed with strontium ranelate treatment

is due just to the physical presence of strontium in bone, but he cautions that there is ample doubt in this estimate. Meanwhile, investigators at the company estimate that only about 50% of the change is due to the physical presence of strontium.

The discrepancy in these estimates stems from a disagreement over a key inference one must make to compensate for a difficulty unique to these BMD studies. "The problem is that we can only take bone biopsies from one site, the iliac crest, but the measurements of bone density made with our scanning machines are at the spine and hip," says Dr. Blake. "We can only tie the two together if we know what the typical ratio is of strontium concentration in the hip or spine to the pelvis." The value of this ratio cited by researchers at Servier is lower than Dr. Blake's value, thus accounting for the substantial differences in their estimates.

#### **Potential Molecular Mechanisms of Action**

Observers on both sides of the argument acknowledge that the anti-fracture efficacy of strontium ranelate demonstrated in the clinical trials is the most salient fact. Debate, then, about the causes of the BMD changes and thus about the underlying mechanisms of the drug's actions is perhaps not of central concern. However, while unlikely to change the way strontium ranelate is used and prescribed right now, understanding underlying mechanisms may still have a high degree of scientific import. Indeed, if the bone field is searching for an agent that simultaneously decreases resorption and increases formation, and if strontium ranelate does accomplish this to some degree, understanding how the drug actually works may help to advance the development of future "holy grail" osteoporosis drugs, and perhaps even suggest a way to make strontium ranelate itself more effective.

To explain the potential bone-building activity of strontium ranelate, one area of investigation has provided evidence for a role of prostaglandins. Recent research *in vitro* by Dr. Raisz and colleagues, funded by Servier, suggests that strontium ranelate treatment of bone marrow stromal cells

stimulates the differentiation and mineralization of those cells through an effect on prostaglandins, since pharmaceutical blocking of the COX-2 enzyme necessary for prostaglandin production prevented these changes, as did genetically knocking out the gene for the enzyme. Another line of inquiry has examined the ability of strontium ranelate to activate the calcium-sensing receptor. For instance, recent research by Edward Brown and colleagues found that strontium ranelate stimulated the proliferation of rat primary osteoblasts, an effect that was significantly less in osteoblasts transfected with a dominant-negative calcium-sensing receptor. However, there is also evidence from studies performed by Darryl Quarles and colleagues to suggest that there may be at least one other strontium-sensing receptor in bone cells.

Some experts note that strontium ranelate probably acts in a modest way on each of multiple mechanisms, and perhaps the tolerability of the drug, and its clinical effects, stem from the sum of these small effects, including alterations of prostaglandin production; the involvement of the calcium-sensing receptor; perhaps modest changes in bone remodeling; perhaps the physical presence of strontium in bone; and perhaps yet undiscovered mechanisms. "Which one of these mechanisms prevails or predominates or accounts for most of strontium ranelate's anti-fracture efficacy? I really don't think anybody knows," says Dr. El-Hajj Fuleihan.

Supporters of the drug note that it is not strange that so much remains uncertain, considering that strontium ranelate is still a relatively new drug. In fact, perhaps some of the criticism of strontium ranelate is unfair: when it can take many years both to translate data *in vitro* and animal findings into human studies and to definitely pin down mechanisms of action, should a lack of convincing answers on these issues be the basis of criticism? Perhaps not, yet when the drug is billed as the first osteoporosis agent to inhibit resorption and build new bone at the same time—a goal that, if reached, an entire field agrees will be a quantum leap forward in osteoporosis

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treatments of the future—perhaps it is also not strange that widespread skepticism is currently the ruling order of the day.