Strontium Ranelate in the Healing of Fractures Complicated with Delayed Union. It is Really Effective?

PAUL DAN SIRBU[1], RAZVAN TUDOR[2]*, VLAD VERINGA[1], BOGDAN MIHNEA CIUNTU[3]*, VALENTIN RADU[1], BOGDAN CIUBARA[5]*, OANA VIOLA BADULESCU[4]

[1]Grigore T. Popa University of Medicine and Pharmacy, Faculty of Medicine, Department of Orthopedics and Traumatology, Surgical Sciences (II), 16 Universitatii Str., 700115, Iasi, Romania

[2]Vaslui County Hospital, Department of Orthopedics and Traumatology, 233 Stefan cel Mare Str. 730006, Vaslui, Romania

[3]Grigore T. Popa University of Medicine and Pharmacy, Faculty of General Medicine, Surgery Department, 16 Universitatii Str., 700115, Iasi, Roman

[4]Grigore T. Popa University of Medicine and Pharmacy, Faculty of Medicine, Department of Pathophysiology, Morfo Functional Sciences (II), 16 Universitatii Str., 700115, Iasi, Romania

[5]Dunarea de Jos University, Faculty of Medicine and Pharmacy, Departament of Morphological and Functional Sciences, 35 Al. I. Cuza Str., 800010, Galati, Romania

Osteoporosis is a systemic skeletal disease characterized by low bone strength, which leads to an increased risk of fracture. The primary objective of osteoporosis treatment is the prevention of fragility fractures and the secondary objective is their rapid healing if they occur. Strontium ranelate is an antiosteoporotic therapeutic agent with a double action mechanism: the increase of bone formation and the decrease of bone resorption, contributing thus to the improvement of bone healing. Preclinical studies have demonstrated the efficacy of strontium ranelate for the improvement of bone healing and bone microarhitecture, as well as of the osteointegration of implants. Some clinical cases have been reported regarding the efficacy of strontium ranelate in the healing of long bone fractures complicated by nonunion or delayed union. In the present study we have reported 2 clinical cases that demonstrate the effectiveness of the treatment with strontium ranelate (Osseor) for 3-6 months in the healing of complicated long bone fractures with delayed union. Our cases confirm the results of the open label study CL3-12911-036 (delayed union and non-union fracture study), where the treatment with 2 g/day of strontium ranelate improved healing and led to a better quality of life. Even if there are some cardiovascular contraindications, strontium ranelate is proven to reduce vertebral and non-vertebral fracture risk in osteoporosis and in the same time improves bone microarchitecture and accelerates fracture healing.

Key words: Strontium ranelate, osteoporosis, bone formation, delayed union, fragility fractures

Osteoporosis is a systemic disease commonly seen in elderly patients, characterized by a reduction in bone mineral density (BMD) combined with the alteration of the trabecular structure, which predisposes the bone to fractures as a result of low-intensity traumas [1,2].

The prevention of fragility fractures is the main goal of the osteoporosis treatment. The two major classes of drugs [1] in use are: a) antiresorbent agents that block bone resorption by inhibiting osteoclast activity; b) anabolic agents that stimulate bone formation by acting primarily on osteoblasts.

If a fracture occurred, rapid and good quality healing (problematic in elderly patients with osteoporosis) is a very important desideratum. However, the role of anti-osteoporotic drugs in the healing of fragility fractures is insufficiently known nowadays.

Strontium ranelate

Strontium ranelate is a therapeutic agent made of 2 stable strontium atoms attached to an organic core consisting in ranelic acid. It is composed of an organic molecule, ranelic acid, which binds the two stable strontium atoms.

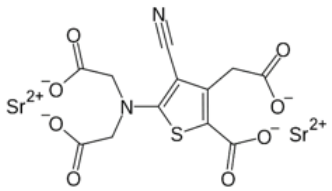

Fig. 1. Chemical formula of sodium ranelate

Strontium ranelate has shown its effectiveness in reducing the risk of spine or hip fracture in women with postmenopausal osteoporosis [3,4]. Multiple evidence suggests that strontium ranelate has varied effects on bone metabolism. Its use in the treatment of osteoporosis, based on a double action mechanism, consists in: increased bone formation and decreased bone resorption. Due to this unique action mechanism, strontium ranelate appears to be the most physiological of all antiosteoporotic agents. It differs from antiresorptive agents that inhibit bone resorption (with a concomitant reduction in bone formation), as well as from osteoformers (which increase bone formation together with bone resorption) [5, 6].

The cellular and molecular mechanisms of strontium have been recently identified. On the one hand, strontium ranelate stimulates the replication of preosteoblasts in

* *email: rc_tudor@yahoo.com; bogdanmciuntu@yahoo.com; abciubara@yahoo.com*

osteoblasts, leading to an increase in organic matrix synthesis, while on the other hand, strontium ranelate inhibits the differentiation of preosteoclasts in osteoclasts and decreases resorptive bone activity (fig. 2]. At the same time, there are studies showing that the fixation of strontium on the bone surface is effective in blocking osteoclastic bone resorption, without any apparent cytotoxic effect on the osteoclasts, while their attachment and viability are normal [6].

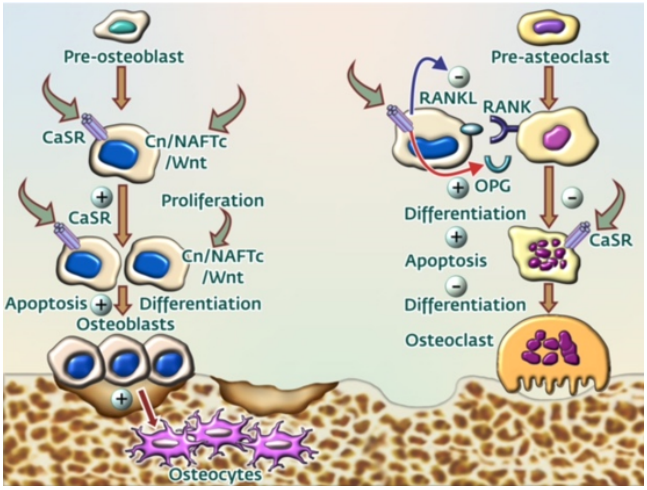

Fig. 2 Action mechanism of strontium ranelate, adapted from: Marie PJ et al, Osteoporos Int. 22: 1659, 2011 [7]

Preclinical studies have demonstrated the efficacy of strontium ranelate in improving bone healing and microarhitectometry, as well as the osteointegration of implants[8-11]. Several clinical cases have been reported regarding the efficacy of strontium ranelate in the healing of long bone fractures complicated by nonunion or delayed union [12, 13]. In fact, in september 2014, professor JM Feron, reported the 12-month results of the *delayed and non-union fracture* study, CL3-12911-036 [14]. This open label study on 48 patients, concluded that the treatment with strontium ranelate(2g/day) for 12 months improved the healing of long bone or clavicle fractures complicated by aseptic nonunion or delayed union. The favorable effect on fracture healing has been associated with pain reduction, obvious functional improvement and increased quality of the patient's life.

Unfortunately, the use of strontium ranelate is now restricted to the treatment of severe postmenopausal osteoporosis in women, but also in adult men with a high risk of fracture, when treatment with other osteoporosis drugs is not possible due to contraindications or intolerance. Cardiovascular contraindications for the use of strontium ranelate include: patients with established, current or past history of ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease or uncontrolled hypertension [15].

The aim of this study is to present two personal clinical cases where strontium ranelate (2g/day) improved healing in fractures with delayed union.

Clinical Cases

Case 1

M.L., 50 years old, female, distal left tibial shaft combined with fracture of medial malleolus; close reduction and locked intramedulary nailing for distal tibia, percutaneous screw on medial malleolus; delayed union for tibial fracture at 3 months postoperative with pain at weight bearing. Starting the treatment with SR (Oseor 2g/day) + Calcium and D vitamin for 6 months. Calus formation at 12 months with Strontium Ranelate 2g/day [fig. 3].

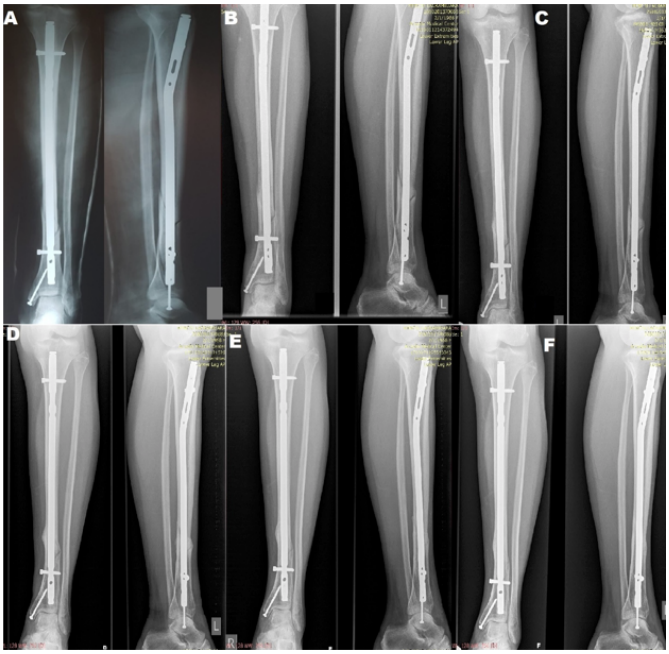

Fig. 3. A-C. A-Immediate postoperative X-ray; B-3 months X-ray with delayed union of tibial fracture; starting the treatment with SR; C-6 months X-ray with evidence of bony bridging callus at the fracture site; D-8 months X-Ray, E-10months X-ray, F-12 months X-ray; D-F: Evident progressive bridging callus with nice healing and bone remodeling at 12 months

Case 2

C.C., 48 years old, male, distal femural shaft fracture, open type II Gustillo (operated in another department with external fixation and then with a short locked plate; secondary displacement with failure of the construct at 2 months postoperatively). Reoperated with a longer locked plate, bone graft from iliac crest and synthetic bone substitute; starting treatment with Osseor at 1,5 postoperative due to minimally appearence of callus. Progressive bridging callus with nice healing at 6 months postoperatively [fig. 4].

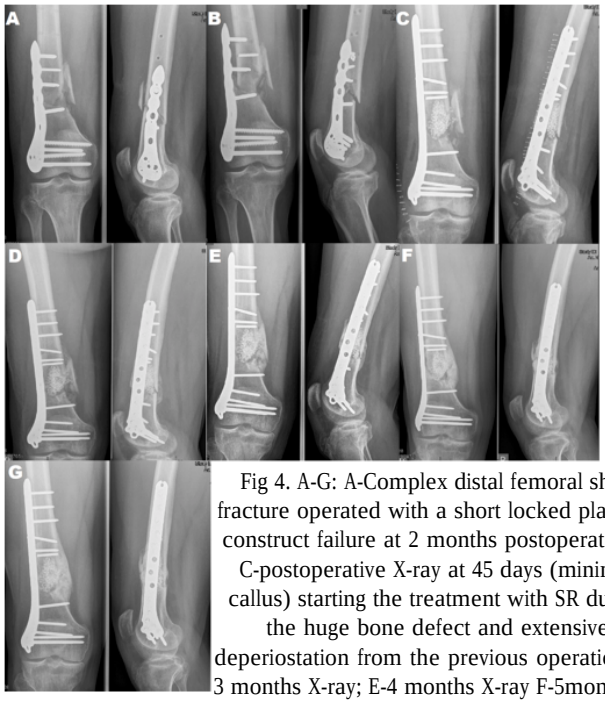

Fig 4. A-G: A-Complex distal femoral shaft fracture operated with a short locked plate; B-construct failure at 2 months postoperatively; C-postoperative X-ray at 45 days (minimal callus) starting the treatment with SR due to the huge bone defect and extensive deperiostation from the previous operation. D-3 months X-ray; E-4 months X-ray F-5months X-ray G-6 months X-ray
D-G: Progressive bridging callus formation with nice healing at 6 months postoperatively

Results and discussions

Osteoporosis is a major public health problem. Its main clinical manifestation and complication are fragility fractures that increase morbidity and mortality [1, 2, 16, 17]. The healing process of fragility fractures is determined by age and bone quality. It is much slower in the case of the elderly due to cellular and molecular changes, which affect the healing phases [11, 18, 19]. Studies on fracture healing performed in mice have concluded that cartilage and bone formation are delayed in elderly animals, and the callus mineralization is reduced [10,20,21].

Anti-osteoporotic agents have different modes of action and can adversely affect consolidation by impairing the proliferation of early callus, the differentiation of chondrocytes or osteoblasts and the formation of capillary vessels [22]. For this reason, the ideal antiosteoporotic drug would be the one that improves BMD and reduces the risk of fracture, ensuring at the same time the consolidation of fractures, if they occur [10,11]. In fact, the crucial concept in skeletal metabolism is represented by the coupling between bone formation and resorption [10]. There are studies that conclude that many antiosteoporotic drugs (bisphosphonates, teriparatide PTH and calcitonin) can affect the healing process [23,24]. Strontium ranelate is the only antiosteoporotic treatment with double action mechanism: It increases bone formation and decreases bone resorption. In addition to improving the activation of osteoblast replication and reducing osteoblast apoptosis [25,26], strontium ranelate inhibits osteoclast activity, as well [27]. Strontium ranelate has proven to be effective in bone healing by improving bone remodeling, which results in improved microarchitecture and intrinsic tissue quality [28].

In comparison to alendronate, strontium ranelate causes an increase in cortical thickness and trabecular density over a period of 1 year. [13] After several tests, this study concluded that strontium ranelate improves bone microstructure over a period of 3 months, while alendronate maintains the same bone structure and does not allow its degradation.

Besides healing fractures faster, strontium ranelate, in doses of 1 or 2 g/day, has been associated with a significant improvement in bone microstructure in the case of patients with gonarthrosis. A significant decrease in symptoms has been observed with doses of 2 g/day [13].Strontium ranelate has been studied for a period between 5 [29] and 8 years [30] in animals and humans. It has demonstrated its efficacy in both, bone regeneration with preosteoblast replication and the decrease of bone destruction by osteoclast inhibition.

Various studies performed in animals have shown that some osteoporosis drugs can also be used to heal fractures, because they have influence on this process. Studies in rats with densitometric, biomechanical, histological, micro-CT and radiological results have shown that a daily dose of 625mg/kg of strontium ranelate (2g/day for humans) has anabolic effects on osteoblasts. These studies in ovariectomized mice reveal an increase in callus volume and biomechanical resistance, with no negative effect on those mice that were not ovariectomized during the study, which healed naturally [31].

Another comparative study evaluated the healing of fractures under treatment with strontium ranelate and PTH 1-34 in ovariectomized mice vs. untreated rats, which healed naturally. Both strontium ranelate and PTH helped to increase trabecular bone volume with callus formation, but only strontium ranelate led to an increase in resistance during torsional tests. The findings of this study show that strontium ranelate is superior to PTH treatment [32].
A clinical trial containing 2 cases with fractures at different levels, with healing delay, demonstrated the efficacy of strontium ranelate and its effect not only on osteoporosis, but also on the healing of fractures, due to its dual effect of forming new bone tissue and inhibiting bone destruction by osteoclast apoptosis. The authors of this study recommend a more frequent use of strontium ranelate in a greater variety of fractures, because its benefits and superiority to other antiosteoporotic drugs have been demonstrated. [10].

Strontium ranelate has demonstrated its efficacy in a another study based on 4 clinical cases of patients aged between 25 and 63 with fractures of long bones, at different levels, which did not consolidate after 12 months, but consolidated after in 3-6 months under treatment with strontium ranelate 2g/day. [11]

All these cases with isolated fractures were considered to be healed taking into account the absence of pain (especially with support) and the appearance of radioglogic callus (Corrales LA).

The open-label study CL3-12911-036 on 48 patients titled 12-month Results of the Delayed and Non-Union Fracture Study concluded that treatment with strontium ranelate (2g/day) improved the healing of long bone or clavicle fractures complicated by delayed union or nonunion. [14] Improved healing has been materialized by reduction of pain and the improvement of limb functionality and life quality.

The cases presented by us confirm the results of study CL3-12911-036 and support the effectiveness of strontium ranelate (Osseor) treatment for 3-6 months in the healing of long bone fractures complicated by delayed union.

Conclusions

Strontium ranelate is an antiosteoporotic therapeutic agent with a double action mechanism: the increase of bone formation and the decrease of bone resorption, contributing thus to the improvement of bone healing.

In the present study we have reported 2 clinical cases that demonstrate the effectiveness of the treatment with strontium ranelate (Osseor) for 3-6 months in the healing of complicated long bone fractures with delayed union. Our cases confirm the results of the open label study CL3-12911-036 (*delayed and non-union fracture* study), where the treatment with 2 g/day of strontium ranelate improved healing and led to a better quality of life.

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