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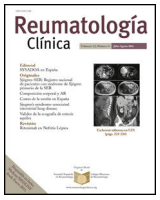

Special Article

Position of the Spanish Society of Rheumatology (SER) and the Spanish Society for Bone Research and Mineral Metabolism (SEIOMM) on romosozumab☆

Posicionamiento de la Sociedad Española de Reumatología (SER) y la Sociedad Española de Investigación Ósea y Metabolismo Mineral (SEIOMM) respecto a romosozumab

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In this joint position paper by the Spanish Society of Rheumatology (SER) and the Spanish Society for Bone Research and Mineral Metabolism (SEIOMM) on romosozumab, we analyse the reasons why we consider that this drug provides a significant therapeutic advantage and, therefore, should be incorporated into the pharmacotherapy available in our country for the management of osteoporosis, especially severe osteoporosis.

In summary, romosozumab has the following properties:

- It has a novel and unique mechanism of action.
- It induces a faster and greater increase in bone mineral density in the lumbar spine and femur than other osteoporosis drugs.
- It rapidly and significantly reduces the risk of different types of fractures, both in monotherapy and in sequential treatment with denosumab and alendronate.
- It has an adequate safety profile, as endorsed by EMA approval, with the corresponding restrictions in patients at increased cardiovascular risk.
- For all these reasons, romosozumab improves the treatment of osteoporosis, especially in patients with fractures and markedly decreased bone mineral density, in whom there is a notable increase in the risk for fracture.

Romosozumab is a humanised IgG2 monoclonal antibody that binds to and inhibits sclerostin, a protein expressed mainly by osteocytes, with high affinity and specificity, which gives it a unique dual effect on bone homeostasis, as it simultaneously actively stimulates bone formation and inhibits resorption[1–3].

Romosozumab promotes the transformation of bone lining cells into active osteoblasts, increases extracellular bone matrix production and amplifies the recruitment of osteoprogenitor cells, all of which increase bone formation[4–6]. It simultaneously decreases resorption by acting on the osteocyte expression of osteoclast mediators such as OPG, RANKL, CSF-1, and WISP1[5,7]. This dual and singular effect of romosozumab causes an increase in bone formation, especially trabecular and cortical bone, with a positive net end result[6,8].

Romosozumab has a rapid effect, reaching its C_{max} in 5 days, with a half-life of around 13 days. Its effect is reversible, as the

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changes it causes in bone turnover markers, especially in procollagen type I amino-terminal propeptide, tend to normalise 12 months after initiation of treatment[1].

The increase in bone mineral density at the lumbar spine and femur with romosozumab is more rapid and greater compared to the other osteoporosis drugs. The increase is 13.3% at the lumbar spine, 6.9% at the femoral neck, and 5.9% at the total hip after one year of treatment compared to placebo[9].

The increase in bone mineral density obtained with one year of treatment with romosozumab followed by one year of denosumab is similar to that achieved with 7 years of denosumab according to the FREEDOM study and its extension studies[10]. Thus, treatment with romosozumab for one year, followed by one year of denosumab (FRAME study), or 2 years of alendronate (ARCH study), induces an increase in bone mineral density of 17.6% and 14.9% in the lumbar spine, and 8.8% and 7% in the total hip, respectively[9,11].

The significance of this marked increase in bone mineral density has recently been validated in a meta-regression analysis of individual data from multiple randomised studies of osteoporosis drugs, including 91,779 patients. This analysis concludes that bone mineral density is a valid surrogate outcome parameter for fracture and that changes in hip bone mineral density explain 44%–67% of the reduction in fracture risk achieved with treatment[12].

Romosumab rapidly and significantly reduces the risk of vertebral fractures and clinical fractures in monotherapy at 12 months, and of all types of fractures in sequential treatment, both with denosumab and with alendronate in the long term.

Treatment with romosozumab has been shown to reduce the risk of vertebral fracture both in naïve patients (72% versus placebo in the FRAME study) and in patients previously treated with alendronate (47% versus alendronate in the ARCH study) 12 months after starting treatment[9,11]. The decrease in the risk of non-vertebral fracture was significant in sequential treatment at 24 months (25% romosozumab/denosumab vs. placebo/denosumab and 19% romosozumab/alendronate vs. alendronate) and in hip fractures the risk was reduced to 41% in the 36-month extension of the FRAME study[9,11,13].

It is important to highlight that due to its mechanism and duration of action, the results of monotherapy with romosozumab are limited to 12 months, compared to the 18–36 months at which the primary objective of reducing the risk of fractures in anti-osteoporotic drugs is set. Hence the importance of considering the sequence of treatments and their differences in the medium/long term. In fact, the reduction in the risk of non-vertebral fractures in monotherapy with romosozumab was 25%–26% at 12 months, in the FRAME study and in the ARCH study, which places it at the limit of statistical significance[9,11].

Non-cardiovascular adverse events recorded after at least one dose and for up to 12 months of treatment were balanced between the romosozumab treatment groups (6002 patients in the ARCH, FRAME, STRUCTURE, and BRIDGE studies) and the comparator groups (5985 patients on alendronate, denosumab, teriparatide or placebo)[11,14–16]. Non-cardiovascular adverse effects occurring in more than 5% of subjects in clinical trials with romosozumab include arthralgia and headache. Approximately 5% of subjects have reactions at the site of the first injection; however, this adverse event does not seem to recur with subsequent injections[17]. Other serious adverse events, including osteonecrosis of the jaw and atypical femur fractures, which are of concern with drugs that decrease bone resorption, should be of minor concern with romosozumab[14–17].

Non-specific, non-cardiovascular events included low back pain, which occurred in 19.5% of patients on alendronate and 16.1% of patients on romosozumab, followed by alendronate in the ARCH study, and in 14.4% of patients on placebo/denosumab and 12.9% of patients on romosozumab/denosumab in the FRAME study[11,14]. Arthralgias were also frequent in both groups, 15.8% vs. 16.3%, and 10% vs. 6%. Local injection site reactions (injection site pain, erythema, pruritus, bleeding, rash, and swelling) were generally mild and none were considered serious. Anti-romosozumab antibodies appear in about 15% of patients (15.3% in ARCH and 18% in STRUCTURE and neutralising antibodies in only .6% in ARCH and .7% in FRAME, with no detectable effect on drug efficacy or safety)[11,14,15]. In the FRAME trial, 2 cases of osteonecrosis of the jaw were reported (one in the romosozumab group and one in the romosozumab followed by the denosumab group) with reservations of causal adjudication[14]. In the ARCH trial, there were no cases of osteonecrosis of the jaw in the first year of treatment. However, 2 cases were reported in the second 12-month period (one in the alendronate/alendronate group and one in the romosozumab/alendronate group)[11]. As a precaution, the product label suggests that patients initiating treatment with romosozumab should have a routine oral examination before starting the drug. Atypical femur fracture was reported in one case receiving romosozumab in the FRAME trial, with confounding factors as to the cause due to the presence of prodromal pain in the area at the time of recruitment[14]. In the ARCH study, no atypical femoral fracture events were reported in the 12-month double-blind period, although 6 atypical femoral fracture events were positively adjudicated during the open-label period (2 [<.1%] in the romosozumab to alendronate group and 4 [.2%] in the alendronate to alendronate group).

The cardiovascular safety of romozosumab in postmenopausal women with osteoporosis has been assessed in 2 large clinical trials (FRAME and ARCH trials). Compared to placebo (first year of the FRAME trial) no differences in serious cardiovascular events recorded as MACE were identified (HR: 1.03 [.62–1.72])[9]. Compared to alendronate (first year of the ARCH trial) an imbalance was identified (HR: 1.87 [1.11–3.14])[11]. A meta-analysis of both trials showed no difference (HR: 1.39 [.97–2.00])[18]. The number of cardiovascular events was very low in both studies.

Sclerostin is expressed in the smooth muscle of vascular tissue. However, inhibition of sclerostin in preclinical models or rare genetic diseases has not been shown to be associated with unfavourable cardiovascular outcomes[19]. Clinical trials with romozosumab have not been designed to assess cardiovascular safety, and show discrepant and inconclusive results on the risk for cardiovascular events. Follow-up of these patients after discontinuing the drug does not change the incidence of these events, which calls into question their causal relationship. Furthermore, the low event rate increases the likelihood that the findings are due to chance[20]. The European Medicines Agency (EMA) has currently contraindicated the use of romozosumab in patients with a history of acute myocardial infarction or stroke. Real-life and pharmacovigilance studies are ongoing to learn more about this issue. Clinicians should adhere to the label specifications and assess the risk/benefit ratio on a case-by-case basis.

What does it contribute to the treatment of osteoporosis? A window of opportunity

Romosozumab is particularly indicated in patients with severe osteoporosis, associated with fractures, in whom there is also markedly decreased bone mineral density and no contraindications for its use.

Romosozumab improves the therapeutic approach to osteoporosis and, in particular, to severe osteoporosis, i.e., those patients with fractures and markedly decreased bone mineral density. In this type of patient, in whom there is a notable increase in the risk for fracture, romosozumab has demonstrated greater anti-fracture efficacy when compared with an active treatment such as

alendronate, considered the first-line therapy in postmenopausal osteoporosis. Thus, romosozumab has demonstrated not only a greater increase in bone mineral density in all the skeletal sites analysed, more than 13% in the lumbar spine at one year of treatment (equivalent to standard deviation 1 on the T-score) and around 7% in the total hip, but also a greater decrease in the incidence of vertebral, non-vertebral and femur fractures[11].

Notably, this marked increase in bone mineral density is achieved after only one year of treatment, reaching an increase of 18% at 2 years (after one year of additional sequential treatment with denosumab); that is, with only 2 years of treatment (one year of romosozumab, followed by one year of denosumab), increases in bone mineral density are achieved, both in the lumbar spine and in the proximal femur, similar to those obtained with 7 years of continuous treatment with denosumab, a drug with recognised anti-fracture efficacy and which has been associated with a considerable increase in bone mineral density[9,10]. The relevance of these results lies in the relationship between the increase in bone mineral density produced by a drug and its anti-fracture effect, since the greater the increase, the greater the anti-fracture efficacy. In this regard, and based on recent studies including several clinical trials with different drugs (analysing more than 90,000 patients by meta-regression analysis), increases in bone mineral density of 2% in the lumbar spine have been associated with a decrease in the incidence of vertebral fractures of around 28%, whereas if the increase is 14% this decrease would be close to 80%, with similar data in the total femur, where an increase in bone mineral density of 2% is associated with a decrease of 16% in hip fracture, and if it is 6% the decrease would be in the order of 40%[21].

It is also important to remember that there are various factors related to the risk of fracture, including having suffered a previous fracture, the risk being particularly high when the fracture is recent (especially during the first 2 years), and when it is a vertebral or femoral fracture. This "very high risk for fracture" indicates the need not only to institute anti-osteoporotic treatment, but also to select the most effective treatment in this type of patient. As mentioned above, treatment with romosozumab achieves the greatest increase in bone mineral density in the shortest period. After one year of treatment with romosozumab followed by one year of treatment with an antiresorptive, either denosumab or alendronate, increases in bone mineral density are achieved with which a reduction in the incidence of vertebral and femur fracture of 80% and 40%, respectively, has been estimated, achieving the therapeutic end point quickly in the patients at greatest risk[11]. An additional advantage is that this drug can be used in patients who have previously been treated with teriparatide (or vice versa), making it a particularly useful therapy in those individuals with fractures and very low bone mineral density, with a T-score $\leq$3.5 or $-$3, in whom achieving a bone mineral density $\geq$2.5 or $-$2 (a therapeutic end point proposed by various scientific societies) can be almost impossible with the majority of antiresorptive drugs currently in use[22,23]. It should also be remembered that naïve patients, i.e., those who have not received any other type of previous anti-osteoporotic treatment, show a greater increase in bone mineral density with romosozumab; this aspect makes it necessary to consider the sequence of the different anti-osteoporotic treatments to obtain maximum therapeutic efficacy (a concept known as "sequential treatment")[14,24–26].

The above supports the use of romosozumab as a first line drug in patients with severe osteoporosis at high risk for fracture in whom there are no contraindications for its use. Its indication in patients with a marked decrease in bone mineral density (especially if with a T-score $\leq$3.5) should also be assessed, remembering the importance of the optimal sequence of drugs, in which maximum efficacy is obtained when this therapy is used when treatment is initiated.

Romosozumab is currently approved for the treatment of severe postmenopausal osteoporosis with high fracture risk, although there is evidence of efficacy in other models and clinical settings.

Conflict of interests

Dr Castañeda has received consultancy or lecture fees from Amgen, Grünenthal, Eli Lilly, Stada and UCB; Dr Gómez-Alonso has received consultancy or lecture fees from Amgen, FAES, Grünenthal, Italfármaco, Gebro, Kyowa Kirin and UCB; Dr Graña has received consultancy or lecture fees from UCB. Graña has received consultancy or lecture fees from UCB, Amgen, Grünenthal, Gedeon-Ritcher, Eli Lilly, Gebro and Stada; Dr Guañabens has received consultancy or lecture fees from Amgen, Eli Lilly and UCB; Dr Muñoz-Torres has received lecture fees from Amgen, Eli Lilly and UCB. Dr Muñoz-Torres has received consultancy or lecture fees from UCB, Amgen, Eli Lilly, Stada, Gedeon-Richter, Kyowa Kirin, Meijii, Faes, Grünenthal and Theramex; Dr Peris has received consultancy or lecture fees from Eli Lilly, UCB, Amgen and Kyowa Kirin; Dr Naves has received consultancy or lecture fees from Eli Lilly, UCB, Amgen and Kyowa Kirin. Dr Naves has received consultancy or lecture fees from UCB, Grünenthal and Gedeon-Richter; Dr Alvaro-Gracia has received consultancy or lecture fees from AbbVie, BMS, Eli Lilly, MSD, Novartis, Pfizer Inc, Roche, Sanofi, and UCB.

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