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WHEN SKIN REACTIONS INTERRUPT BONE THERAPY: SEVERE CUTANEOUS ADVERSE REACTION TO ROMOSOZUMAB LEADING TO TREATMENT DISCONTINUATION

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ABSTRACT

Background: Romosozumab is a sclerostin-inhibiting monoclonal antibody that is effective and safe for anabolic treatment in patients with osteoporosis. Its main adverse effects are local; the severity of these injection-site reactions in clinical trials was generally mild.

Case report: We present a case of a 71-year-old Colombian woman with osteoporosis at very high risk of fractures with no relevant history of drug allergies. Bone-forming management was indicated for 12 months with romosozumab after ruling out contraindications and alterations in bone mineral metabolism that would prevent its use. After the first dose of romosozumab 210 mg subcutaneously in the abdomen, she presented a severe local cutaneous adverse reaction, she developed two asymmetric erythematous-oedematous circinate plaques with regular and well-defined borders with a perilesional whitish halo associated with local heat in the umbilical region, which forced the discontinuation of this medication after a joint evaluation with endocrinology, dermatology and allergology. Management was rotated to teriparatide with good tolerance. During follow-up, complete improvement was achieved slowly and progressively, 20 days after the application of romosozumab, without any other related adverse reactions.

Conclusion: This case documents a severe cutaneous reaction at the romosozumab application site, with an atypical presentation due to its extent and intensity, which led to treatment discontinuation. Although these reactions are usually mild, their early recognition is crucial to ensure proper management and avoid complications that could compromise treatment continuity.

KEYWORDS

Adverse drug reaction, romosozumab, skin reactions, osteoporosis, monoclonal antibodies

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LEARNING POINTS

- Severe inflammatory skin reactions can occur at the romosozumab injection site, even in patients without a relevant allergic history.
- The detection of moderate or severe local inflammatory reactions allows for an adequate assessment of the risk-benefit balance of romosozumab treatment, which is essential for deciding whether to discontinue treatment and redirect bone-forming therapy.

INTRODUCTION

Romosozumab is a novel drug positioned as the most potent anabolic therapy for the treatment of osteoporosis[1]. Useful in patients with osteoporosis at very high risk of fractures, this humanized IgG2 monoclonal antibody targets sclerostin, a glycoprotein synthesized in osteocytes that inhibits bone formation. This anti-sclerostin effect has a dual impact on bone metabolism; romosozumab promotes bone formation and reduces resorption[1-6].

Pivotal clinical studies, such as FRAME[2], ARCH[3], and BRIDGE[4], have demonstrated its efficacy. Regarding its safety profile, the most common adverse effects are arthralgia and headache. Initially, particular interest was generated due to the association with an increased risk of major atherosclerotic events[3]; however, recent publications have confirmed the cardiovascular safety of this molecule[7]. Injection site reactions occur in 3 to 5% of patients and are usually mild and transient[2-6].

We describe the case of a 71-year-old patient with severe osteoporosis who developed a large, painful, and persistent inflammatory skin reaction at the romosozumab application site, an adverse event rarely documented in the medical literature. This atypical manifestation required discontinuation of treatment and a switch to another bone-forming therapy. This case highlights the importance of early recognition of these unusual reactions to optimize patient safety and make timely therapeutic decisions.

CASE DESCRIPTION

A 71-year-old female with a history of multiple autoimmune diseases (systemic lupus erythematosus, Sjögren's syndrome, primary biliary cirrhosis, and autoimmune hypothyroidism) and severe postmenopausal osteoporosis. She had no history of underlying cardiovascular events. She presented with a fragility fracture, a fall from her standing height, with collapse of the L3 vertebral body, with a 65% loss of the central portion's height, as well as residual retropulsion of the posterior wall, generating narrowing of the canal at L3-L4, L4-L5, and L5-S1, for which neurosurgery performed vertebroplasty. She was referred to endocrinology for evaluation. Secondary pathologies such as hyperparathyroidism, hypercortisolism, acromegaly, multiple myeloma, or alterations in the calcium, phosphate, and vitamin D profile were ruled out. Dexa bone densitometry (Hologic®) L1-L2 spine bone mineral density: 0.734 TS: -3.7 ZS: -2.1. Left femoral neck: bone mineral density (BMD): 0.642 TS: -2.8 ZS -1.1. Left total hip: BMD: 0.616 TS: -3.1 ZS: -1.6. Given bone involvement, it was decided to start with the osteoformant romosozumab 210 mg 1 subcutaneous dose monthly for 12 months (rotating application site). After the first application, the patient began to present inflammatory signs at puncture sites, of a non-infectious type, without associated systemic symptoms *(Fig. 1)*.

An adverse drug reaction was considered; the patient had no history of relevant drug allergies, and a previous allergy to thimerosal and nickel was diagnosed for cosmetic use, which are not part of the excipients described in romosozumab. The case was evaluated jointly by the allergist and dermatologist, who decided not to continue the treatment. The patient was replaced with teriparatide (an injectable osteoforming agent), which was currently in use, with no adverse effects reported by the patient. The patient's clinical findings improved with topical corticosteroids (hydrocortisone 0.1% for 7 days) and moisturizing with aluminium acetate lotion and completely resolved by day 20 of progression *(Fig. 2 and Fig. 3)*.

DISCUSSION

Currently used anabolic drugs can be classified into two groups according to their mechanism of action: parathyroid hormone analogues such as teriparatide and abaloparatide, which are capable of inducing new bone formation; however, they also activate bone resorption, which decreases the net balance of bone formation[1]. On the other hand, sclerostin inhibitors act differently[7-8]. Romosuzumab is a humanized IgG2 monoclonal antibody that binds to sclerostin, preventing



Figure 1. On the abdomen, asymmetric erythematous-oedematous circinate plaques with regular and well-defined edges and a perilesional whitish halo associated with local heat are observed.

the binding of this protein to the LRP-5 receptor[1-4]. This allows the activation of the WNT signalling pathway, favouring the production of β-catenin and translocation to the nucleus, which stimulates osteoblast differentiation, proliferation, and survival[6,7]. As a result, new bone formation occurs on the trabecular and cortical surfaces. It simultaneously reduces bone resorption, conferring dual activity: osteoformative and antiresorptive[6,7].

Romosuzumab is administered subcutaneously at a monthly dose of 210 mg for 12 months, reaching stable concentrations by the third month. It doubles the formation of bone formation markers and reduces resorption markers by 30% in the first month of use[2-5]. In phase 2 and phase 3 studies, romosuzumab was shown to significantly increase bone mineral density in the spine and hip[8]. Compared with placebo, a 73% reduction in the risk of vertebral fractures, a 36% reduction in clinical fractures, and a 25% reduction in the risk of vertebral fractures was found[2-5]. Compared with alendronate, a 37% reduction in vertebral fractures, a 27% reduction in all fractures, a 38% reduction in hip fractures, and a 19% reduction in non-vertebral fractures was observed. Compared with teriparatide, a significant increase in bone mass of 3.2% was observed in the total femur and a significant increase in the lumbar spine after one year of treatment[6].

The most common adverse reactions associated with the use of romosuzumab, reported in more than 5% of patients, include arthralgia and headache[2-5]. Cases of hypocalcaemia, atypical subtrochanteric and diaphyseal femoral fractures, osteonecrosis of the jaw, and hypersensitivity reactions, including angioedema, erythema multiforme, dermatitis, rash, and urticaria, have also been reported[6]. Regarding cardiovascular safety, the ARCH study conducted in women with postmenopausal osteoporosis found a higher occurrence of death and major cardiovascular events (composite of heart attack, cerebrovascular event, and death from cardiovascular causes) in romosuzumab vs alendronate[3]; additionally, the BRIDGE study conducted in men found an increase in cardiovascular events in patients receiving romosuzumab compared to placebo[4]. A pharmacovigilance study based on data from the FDA FAERS system found a higher rate of major cardiovascular events associated with romosuzumab, especially in Japan[7]; however, a more recent systematic review and meta-analysis found no statistically significant differences in the rate of cardiovascular events compared to placebo[5].

A recent meta-analysis that included 6 placebo-controlled clinical trials evaluated the efficacy and safety of romosuzumab in patients with osteoporosis[9]. The study found that injection site reactions were significantly more frequent in the romosuzumab group compared to the placebo group. These reactions were generally mild. A total of 220 of 4,100 patients receiving romosuzumab experienced local skin reactions, with an 83% increase in the likelihood of experiencing this type of adverse event compared to placebo[9]. In a prospective cohort study conducted in Japan,

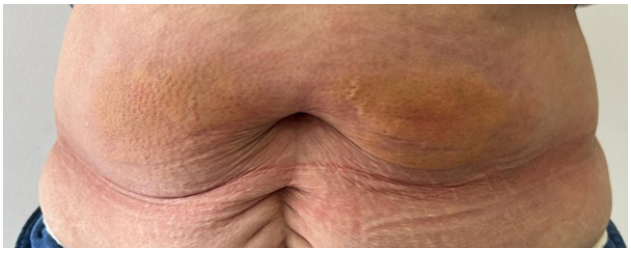


Figure 2. On the abdomen, erythematous yellow circinate plaques with slight persistent oedema with regular and well-defined edges are observed.



Figure 3. Light brown macules with irregular and poorly defined edges in the resolution phase.

adverse reactions occurred in 27.8% of patients receiving romosuzumab, although only 4.3% required discontinuation of treatment. Injection site reactions occurred in 13.9% of patients, the most common being pain, swelling, and erythema lasting 2 days or more[10].

The case presented represents one of the possible cutaneous reactions at the romosuzumab injection site that has not been previously published in the literature. From a dermatological perspective, this is an atypical presentation due to its extent, inflammatory intensity, and duration. The purpose of this report is to document a severe manifestation at the injection site that led to discontinuation of the drug. Although these reactions are usually mild, they can be bothersome for the patient and, as in our case, lead to therapy modification. Early recognition of these reactions is essential to ensure proper management of adverse events.

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