OSTEOPOROSIS

Romosozumab to rebuild the foundations of bone strength

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Biologic agents targeting key proteins involved in bone homeostasis are revolutionizing the management of osteoporosis. New clinical data support the use of these novel therapies to rapidly increase bone mass and decrease the risk of fractures.

Refers to Saag, K. G. et al. Romosozumab or alendronate for fracture prevention in women with osteoporosis. *N. Engl. J. Med.* **377**, 1417–1427 (2017).

Insights into the mechanisms of bone resorption and bone formation have led to the development of biologic therapies that target proteins involved in these processes, such as receptor activator of nuclear factor-κB ligand (RANKL, also known as TNFSF11) and sclerostin, that are transforming the treatment of osteoporosis. The seminal role of sclerostin in the control of bone homeostasis was revealed when mutations in the gene encoding this protein, *SOST*, were found to cause sclerosteosis, a generalized skeletal disorder characterized by bone overgrowth and extremely high bone mass. The results of a clinical trial comparing an anti-sclerostin monoclonal antibody with a long-established therapy for osteoporosis reinforce the clinical potential of targeting sclerostin[1].

Bone formation occurs through two distinct mechanisms, namely bone remodelling, in which osteoblast-mediated bone formation depends on prior osteoclast activity and bone resorption, and bone modelling, in which bone formation is initiated directly by osteoblasts on quiescent bone surfaces. Besides being involved during bone growth, the latter process is stimulated mainly by mechanical forces exerted on the skeleton, which inhibit sclerostin expression by osteocytes, thereby activating the Wnt–β-catenin signalling pathway in osteoblasts[2].

To date, osteoporosis therapy has primarily targeted osteoclasts to inhibit bone remodelling, as is the case with bisphosphonates and the RANKL inhibitor denosumab[3]. Alternatively, the parathyroid hormone (PTH) analogue teriparatide and, more recently, the PTH-related protein analogue abaloparatide have been used to exert bone-forming effects with a concomitant increase in bone turnover of variable magnitude (greater with teriparatide than with abaloparatide)[4]. By contrast, targeting sclerostin with a monoclonal antibody, romosozumab, potently stimulates bone formation, primarily through modelling-based mechanisms[5], while simultaneously reducing bone resorption (FIG. 1). This unique mechanism of action has resulted in prominent increases in bone mass[6], and in trabecular and cortical bone volume and strength, in animal models as well as in humans, and compares favourably with teriparatide[7]. However, these studies have also shown that the bone-forming effects of romosozumab are attenuated over time, whereas its anti-resorptive effects persist[6]. The mechanisms underlying this attenuation are not fully understood, but most likely involve bone mechanostatic responses that trigger the overexpression of counter-regulatory molecules, such as Dickkopf-related protein 1, which inhibit Wnt signalling and ultimately osteoblast differentiation[2]. Together with its rapid and prominent effects on bone mass gain, this early attenuation phenomenon explains why romosozumab was used for only 1 year in the clinical trials, before transitioning to another therapy.

Hence, in the Fracture Study in Postmenopausal Women with Osteoporosis (FRAME) trial, which included 7,180 postmenopausal women with osteoporosis, 1 year of treatment with romosozumab increased spine and hip bone mineral density (BMD) from baseline by 13.3% and 6.8%, respectively[8]. As this treatment was followed by 1 year of denosumab therapy, the cumulative gains in BMD at spine and hip over 2 years reached 17.6% and 8.8%, respectively, which would be equivalent to approximately 7 years of treatment with denosumab alone[9]. In the FRAME trial, romosozumab reduced the risk of vertebral fractures by 73% and of clinical fractures by 36% within 12 months compared with placebo. Although the relative reduction in the risk of non-vertebral fractures (25%) did not reach statistical significance in the overall population, this finding could be explained by the lower than expected rate of non-vertebral fracture in a large subgroup of the cohort (individuals from the Latin America region). Indeed, when further analyses were conducted in individuals recruited outside of Latin America, a significant 42% reduction in non-vertebral fractures was observed in this high-risk population within 12 months[8]. Such a reduction in non-vertebral fractures seemed to be greater than that observed in trials of other anti-resorptive drugs, including zoledronic acid and denosumab.

The superior efficacy of romosozumab over an anti-resorptive agent in patients at high risk of fracture has now been demonstrated directly in the Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk (ARCH) trial, which included 4,093 postmenopausal women with severe osteoporosis (that is, with prevalent vertebral fractures)[1]. Study participants were randomly allocated to receive romosozumab or alendronate for 1 year, followed by open-label treatment of all patients with alendronate for up to 2 years. Compared with alendronate, romosozumab increased BMD by approximately 2.5-fold at the spine and 2-fold at the hip in year 1, and vertebral fracture risk was 37% lower at year 1 and 48% lower at year 2. At study completion (median exposure 33 months), the differences between the group initially treated with romosozumab and the group treated with alendronate alone reached –27% for clinical fractures, –19% for

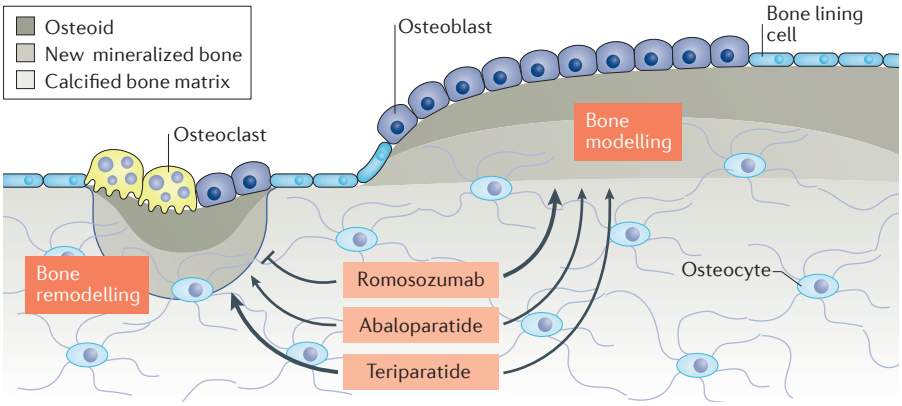

Fig. 1 | **Differential effects of bone-forming agents on bone surfaces.** Teriparatide and abaloparatide act primarily by activating bone formation coupled to bone resorption at remodelling surfaces, and to a lesser extent by activating quiescent bone-forming cells at modelling surfaces. Romosozumab acts primarily by activating modelling-based bone formation while inhibiting bone resorption at remodelling surfaces.

non-vertebral fractures and –38% for hip fractures. It is worth mentioning that in a similar high-risk population, alendronate alone reduced vertebral fractures by 47% and clinical fractures by 28% versus placebo, emphasizing that novel therapeutic approaches starting with romosozumab would provide a true improvement over the already efficacious current standard of care.

Although the findings of the ARCH trial confirm the potential benefits of a sclerostin-neutralizing antibody in patients at high risk of fracture, they also produced some unexpected observations, namely a higher number of adjudicated severe cardiovascular events in the romosozumab group than in the alendronate group (50 versus 38 at 12 months)[1]. Considering the small between-group difference and the fact that no such risk was observed in the previous (and larger) placebo-controlled FRAME trial, it remains unclear whether this apparent adverse event is related to the use of sclerostin inhibition in an older population at high cardiovascular risk; to the protective effects of alendronate in this population, as suggested by some, but not all, previous analyses of alendronate effects on the cardiovascular system[10]; or to chance alone. Notably, in some animal models sclerostin seems to be expressed in the vasculature and in relation to arterial calcifications. To elucidate whether or not sclerostin inhibition might lead to the progression or precipitation of vascular disease is therefore important, particularly because sclerostin inhibitors, by their unique mechanism of action, provide a new hope to eventually treat bone fragility in patients with diabetes mellitus and/or chronic renal failure who also have a high cardiovascular risk.

To conclude, the two major discoveries in bone biology of the past 20 years, namely the essential role of RANKL in stimulating bone resorption and that of sclerostin in inhibiting bone formation, have led in turn to the development of the first two biologics to treat osteoporosis, namely denosumab and romosozumab. If romosozumab becomes available in clinical practice, sequential approaches using these monoclonal antibodies should enable a much larger number of patients to quickly regain bone mass and strength, to the point that a cure for osteoporosis could be foreseen for the majority of patients.

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Competing interests
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