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Romosozumab — on track or derailed?

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Abstract

Romsozumab, a recently developed sclerostin inhibitor, stimulates bone formation and inhibits bone resorption, thereby markedly increasing bone mass and reducing fracture risk. But will a red flag regarding possible adverse cardiovascular events derail this promising new drug for osteoporosis?

The landscape of osteoporosis drugs has changed remarkably over the past three decades. In the late 1980s, the only viable pharmacological options for the prevention or treatment of osteoporosis were oestrogen-replacement therapy for women or calcitonin for women and men. By contrast, in 2017, the options include a range of additional drugs: a selective oestrogen-receptor modulator (SERM; raloxifene); four bisphosphonates (alendronate, risedronate, ibandronate and zoledronic acid); a human monoclonal antibody to the receptor activator of nuclear factor- κ B (NF- κ B) ligand (RANKL; denosumab); and the parathyroid hormone/parathyroid hormone-related peptide analogues teriparatide and abaloparatide, respectively¹.

However, despite this substantial progress, there remains a clear need for new drug development for osteoporosis, particularly if the goal is to reverse, rather than merely prevent, further bone loss. As all currently available drugs, with the exception of teriparatide and abaloparatide, inhibit bone resorption rather than stimulating new bone formation, they have limited efficacy in providing sustained increases in bone mass. Teriparatide and abaloparatide stimulate new bone formation, but this effect wanes over the first few months of treatment, and there is a concomitant increase in bone resorption that limits their efficacy¹. The ‘perfect’ osteoporosis drug would stimulate bone formation over an extended period of time, have no effect on (or reduce) bone resorption, and result in a marked sustained increase in bone mass, thereby offering the possibility of a ‘cure’.

It is in this context that the development of the sclerostin inhibitor romosozumab was anticipated with keen interest. Mutations in the gene that encodes sclerostin, *SOST*, were originally identified as causing sclerosteosis, a rare bone disorder that is associated with high bone mass². Subsequent work demonstrated that sclerostin production is fairly specific to osteocytes embedded in bone, where it inhibits Wnt signalling locally³. Sclerostin

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Competing interests statement

The author declares no competing interests.

neutralization with an antibody activates Wnt signalling, thereby increasing bone formation, inhibiting bone resorption and increasing bone mass both in rodents⁴ and humans⁵. Could this antibody to sclerostin (romosozumab) be the long sought 'cure' for osteoporosis?

Initial studies suggested that it might be. In the phase II study, romosozumab (administered at a dose of 210 mg once monthly) increased spine BMD by 11.3% over just 12 months, compared with a decrease of 0.1% with placebo and increases of 4.1% and 7.1% with alendronate and teriparatide, respectively⁵. Note that the BMD increase with the antiresorptive drug alendronate is not a true anabolic effect (that is, new bone formation), but rather primarily an increase in bone mineralization. With romosozumab, levels of bone turnover markers indicated increased bone formation and reduced bone resorption — perhaps the ideal combination for maximal effects on bone — with the caveat that the bone formation marker increase was transient and returned to baseline by ~6 months. Thus, although not entirely 'perfect' in that the bone formation increase was not sustained indefinitely, romosozumab seemed to come very close to being the ideal osteoporosis drug.

The definitive phase III trial of romosozumab (Fracture Study in Postmenopausal Women with Osteoporosis; FRAME) supported this notion⁶. In 7,180 postmenopausal women with osteoporosis who were randomly assigned to either romosozumab or placebo for 12 months followed by denosumab in both groups for an additional 12 months (to preserve the BMD gains with romosozumab), vertebral fracture risk was 75% lower in women given romosozumab followed by denosumab, than with placebo followed by denosumab⁶. Importantly, adverse events, including cardio vascular events, were similar between groups.

From these key studies, romosozumab seemed poised to fulfil expectations as the ideal osteoporosis drug. That is, until the Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk (ARCH) study by Saag and colleagues was published⁷. To compare efficacy to an established drug (alendronate), ARCH randomly assigned 4,093 postmenopausal women with osteoporosis and a fragility fracture to either 12 months of treatment with romosozumab or weekly treatment with alendronate, followed by open-label alendronate in both groups for an additional 12 months. In skeletal end points at 24 months, romosozumab was clearly superior to alendronate, reducing new vertebral fractures by 48%, clinical fractures by 27% and hip fractures by 38%. Romosozumab was undoubtedly the most potent drug to date for reversing osteoporosis.

The catch came in the form of an unexpected increase in cardiovascular events. Indeed, during the first year, double-blind period, serious cardiovascular events were observed more often with romosozumab than with alendronate (50 of 2,040 patients (2.5%) compared with 38 of 2,014 patients (1.9%); OR 1.31; 95% CI 0.85–2.00)⁷. 16 patients (0.8%) treated with romosozumab had cardiac ischaemic events compared with six (0.3%) treated with alendronate (OR 2.65; 95% CI 1.03–6.77)⁷. Notably, the larger FRAME trial did not identify any imbalance in cardio vascular events in the romosozumab compared with the placebo groups⁶.

One obvious explanation is that alendronate could be cardioprotective. Although conclusive evidence is lacking, meta-analyses of randomized, controlled trials of alendronate have not

found a decrease in cardiovascular events⁸. A second possibility is that the patient populations studied in the FRAME and ARCH trials were fundamentally different. As shown in TABLE 1, women in the ARCH study were, on average, ~4 years older. In addition, 96.1% of women in the ARCH trial had a prevalent vertebral fracture compared with only 18.3% of women in the FRAME trial. As osteoporotic fractures are associated with other ageing co-morbidities, including cardiovascular disease⁹, women in the ARCH trial were clearly less healthy than the women in the FRAME trial. This difference is further reflected in the observed serious cardiovascular events, which were almost twofold higher in the control group (alendronate) in the ARCH trial than in the control group (placebo) in the FRAME trial (1.9% and 1.1%, respectively). Therefore, it is possible that in older, less healthy women with multiple comorbidities and cardiovascular risk factors, a small but still concerning increase in cardiovascular events in response to romosozumab treatment might exist. Indeed, there is biological plausibility for this, as Wnt signalling is known to have an important role in cardiovascular remodelling and sclerostin levels are increased at sites of vascular calcification¹⁰.

In summary, romosozumab is probably the closest we are going to get in the foreseeable future to the perfect osteoporosis drug with respect to skeletal efficacy. The troubling question is whether concern over cardiovascular events will derail its progression to market. Ongoing re-adjudication of the cardiovascular data from the ARCH trial might help resolve this issue. If not, the FDA might approve the drug with appropriate warnings. But, will physicians be inclined to prescribe romosozumab and will patients be willing to accept the small but perhaps real increase in cardiovascular risk in return for its superb skeletal effects? Answers to these questions will undoubtedly define the future of this much-anticipated drug.

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Table 1 |

Population characteristics in FRAME and ARCH trials

	FRAME	ARCH
Mean age (years)	70.9	74.3
Previous vertebral fractures (%)	18.3	96.1
Serious cardiovascular events (%)	<div><div>•</div><div>Placebo: 1.1</div></div> <div><div>•</div><div>Romosozumab: 1.2</div></div>	<div><div>•</div><div>Alendronate: 1.9</div></div> <div><div>•</div><div>Romosozumab: 2.5</div></div>

Data from REFS 6,7.