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NEW AND FUTURE DRUGS FOR OSTEOPOROSIS

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Abstract

This article reviews the results from several recent studies of two novel osteoporosis treatment agents, abaloparatide and romosozumab. Though both agents show promise in fracture risk reduction, the need for further investigation into potential adverse events as well as the need for more head to head trials limit their widespread use in Canada at this time. They are approved in the U.S. and romosozumab was approved for use by Health Canada recently in June 2019, hence patients may ask about them. This article reviews what is known to date.

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Conflict of Interest:

Dr. Stephanie Kim declares no conflict of interest.

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Introduction

Family doctors and geriatricians are often faced with the challenge of treating patients with osteoporosis and fracture histories who have had treatment failures or completed sequential therapy with medicines from different classes. We know anecdotally as well as through studies such as the Global Longitudinal Study of Osteoporosis in Women study (for details of the GLOW study see www.outcomes-umassmed.org/GLOW/) that fractures contribute to a decline in quality of life as much or more than chronic comorbidities such as diabetes, arthritis and lung disease.[1] In addition, many patients are increasingly declining current first-line treatments for osteoporosis due to the increasing public awareness of the rare but serious side effects of atypical femur fractures and osteonecrosis of the jaw.

As we continue to learn more about the different mechanisms of bone loss, drug development and targets for the treatment of osteoporosis have expanded and have led to the introduction of two new pharmacologic agents. This article seeks to shed light on these agents as potential future tools.

Case scenario

Ms. K is a 75-year-old woman you are treating in your Geriatric Medicine clinic who was referred to you for falls. In reviewing her medical history, you note she has had a T12 compression fracture after a fall from standing height. She is taking calcium and vitamin D (to learn more regarding the role of vitamin D see The Role of Vitamin D in Bone Metabolism and Beyond at http://canadiangeriatrics.ca/2014/05/volume-4-issue-1-the-role-of-vitamin-d/).[2] She was briefly treated with risedronate but could not tolerate the GI side effects. Denosumab had been recommended by her family doctor, but she had declined any further treatment, as she was concerned about the possibility of an atypical femur fracture. You review the following as part of an informed discussion with Ms. K (to learn more regarding such concerns see Common Controversies in Osteoporosis Therapy – Helping Patients Make Informed Decisions at http://canadiangeriatrics.ca/wp-content/uploads/2016/11/6_Common-Controversies_Angela-Juby.pdf).[3]

Ms. K had previously considered teriparatide but had not been comfortable with the idea of a daily self-injection. She read about a medication called abaloparatide and wonders how it compares with teriparatide and if it is an option for her.

Abaloparatide

Abaloparatide has been FDA approved for the treatment of osteoporosis in women in the United States since 2017. Similar to teriparatide, it is an anabolic agent, and is a subcutaneous 80 mcg injection administered daily. A one month course of treatment costs approximately $1768 USD. There is also a transdermal patch being studied. Abaloparatide is a 34 amino acid peptide analogue of parathyroid hormone related protein, which binds to parathyroid hormone type I receptor on osteoblasts and osteocytes selectively. This has the overall effect of more transient stimulation of osteoblast cAMP signalling, thereby leading to more anabolic signalling pathway.

The ACTIVE study was a phase 3, international, double-blind, randomized, controlled trial in which 2,463 postmenopausal women with osteoporosis were randomized to receive daily abaloparatide vs. open-label teriparatide vs. placebo for a duration of 18 months, with the primary endpoint being reduction of new vertebral fractures.[4]

In the abaloparatide group, new vertebral fractures occurred in 0.58% of patients vs. 4.22% in the placebo group ($p<0.001$) and 0.84% in the teriparatide group ($p<0.001$). Non-vertebral fractures were also lower in the abaloparatide group compared to the placebo group ($p=0.049$). In addition, those on abaloparatide demonstrated significant increases from their baseline BMD at the total hip (treatment

difference 4.25% [95% CI, 3.90% to 4.59%]), femoral neck (treatment difference, 4.01% [95% CI, 3.58% to 4.45%]) and lumbar spine (treatment difference 10.37% [95% CI, 9.75% to 10.98%]) when compared with placebo (p<0.001). When compared with teriparatide, patients on abaloparatide had greater increases in BMD at sites of cortical bone such as the total hip and femoral neck. Gains in the lumbar spine were only significantly different from teriparatide at 6 and 12 months (p<0.001) but not at 18 months, (p=0.17).[4]

In terms of adverse events, there was no increased risk of osteosarcoma with abaloparatide when compared with teriparatide or placebo. There were more adverse events leading to study discontinuation in the abaloparatide group (9.9%) than in either teriparatide (6.8%) or placebo (6.1%). Serious adverse events, however, were comparable between abaloparatide (9.7%), teriparatide (10%) and placebo (11%). However, the incidence of hypercalcemia was lower with abaloparatide (3.4%) than with teriparatide (6.4%), (p=0.006).

There should be some caution in interpreting these results as the study was not sufficiently powered for a direct comparison of abaloparatide with teriparatide. In addition, the generalizability of these results to our patient population may be difficult, as patients who had been on bisphosphonates for more than three months in the past five years or denosumab within the past year were excluded.

A post-hoc study of women over the age of 80 from the ACTIVE trial showed similar efficacy and safety to younger women.[5]

Ms. K also asks about romosozumab after reading about its recent approval by the FDA and Health Canada.

Romosozumab

Romosozumab represents a new class of osteoporosis medications. It is a monoclonal antibody targeting sclerostin. It is administered as a subcutaneous injection at a dose of 210 mg monthly. The discovery of sclerostin as a potential target arose from studies of van Buchem disease, in which it was noted that the loss of functional sclerostin in these patients was associated with improved bone mass and bone strength.[6] It was thus hypothesized that targeting sclerostin in patients with osteoporosis would increase bone formation and reduce bone resorption. It has recently been approved by the FDA for use in the United States.[7] A one month course of romosozumab costs $1,825 USD. It has also been recently approved by Health Canada.[8]

Several studies have looked at the efficacy of romosozumab. The FRAME study was an international, randomized, double-blind, placebo-controlled trial.[9] Postmenopausal women with osteoporosis were assigned to receive romosozumab for 12 months vs. placebo. Each treatment arm then received denosumab 60 mg SC q six months for another 12 months. The FRAME study demonstrated a 73% lower risk of new vertebral fractures at 12 months in the romosozumab group (risk ratio 0.27; 95% CI 0.16 to 0.47; p<0.001). This effect continued at 24 months in the romosozumab group, with a 75% lower risk of new vertebral fractures after transitioning to denosumab (risk ratio, 0.25; 95 CI 0.14 to 0.40; p<0.001). No significant difference in adverse events was found between the two groups.

The ARCH study was an international, multicentre, randomized, double-blind trial, comparing romosozumab for 12 months followed by alendronate for another 12 months vs. alendronate alone for 24 months for the treatment of postmenopausal women with osteoporosis and at high fracture risk.[10] Compared with patients on alendronate alone, patients who received romosozumab had a 48% lower risk of new vertebral fractures (p<0.001), 27% lower risk of clinical fractures (p<0.001), 19% lower risk of nonvertebral fractures (p=0.04) and a 38% lower risk of hip fractures (p=0.02).

However, there were more serious cardiovascular events associated with romosozumab use, 2.5%,

vs. 1.9% in the alendronate group (odds ratio, 1.31; 95% CI 0.85 to 2.00).[10] Of these cardiovascular side effects, 16 patients (0.8%) in the romosozumab group and six patients (0.3%) in the alendronate group had a cardiac ischemic event (odds ratio, 2.65; 95% CI, 1.03 to 6.77). There was a similar number of reported cerebrovascular events in each group as well (odds ratio, 2.27; 95% CI, 0.93 to 5.22). Because of these findings, the FDA recommends patients who have had a myocardial infarction or stroke in the preceding year not use romosozumab. In Canada, the recommendation is that patients who have had a myocardial infarction or stroke not use romosuzomab. Further studies are needed to better understand this observation, which was not seen in FRAME.

Ms. K thanks you for reviewing future options for osteoporosis treatment but understands that at present, her current treatment options remain unchanged. She agrees to a multidisciplinary approach to falls prevention, to continue calcium and vitamin D and to practice spine sparing strategies and bone strengthening exercises. You refer her to the Osteoporosis.ca website for further patient education (see https://osteoporosis.ca/about-the-disease/).[11] She also understands that she is at high 10-year risk of fracture by CAROC (see www.osteoporosis.ca/multimedia/pdf/CAROC.pdf) of greater than 20%. She understands that her risk for fracture far outweighs the risks of atypical femur fracture, which is rare at 2-78 per 100,000 person-years of bisphosphonate exposure[12] and the risk of osteonecrosis of the jaw at 1.03 per 100,000 person-years.[13] Given her previous GI intolerance of bisphosphonates, she agrees to trial denosumab, which has a similarly rare risk of the above-mentioned adverse side effects, and she will receive 60 mg SC q six months until further options become available in Canada. Though romosozumab has been approved, it is not yet available.

Conclusion

The development of romosozumab and abaloparatide highlights potential for further research and development of novel targets for fracture prevention. Until they are widely approved, bisphosphonates, denosumab and teriparatide continue to remain effective treatments for patients with osteoporosis and at high risk of fractures. For other interventions
(see https://osteoporosis.ca/health-care-professionals/).

This article is not an in-depth review but hopes to spark interest in future treatments for osteoporosis. It is clear that further research and more head to head comparison of treatments is indicated to assist with clinical decision-making.

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