NEW DRUGS

Romosozumab

Approved indication: osteoporosis

Evenity (Amgen)
syringe containing 105 mg/1.17 mL

First published 20 April 2021
https://doi.org/10.18773/austprescr.2021.021

Osteoporotic fractures increase morbidity and mortality so osteoporosis in patients with a high risk of fractures should be treated. In addition to calcium and vitamin D, management of osteoporosis can include drugs, such as bisphosphonates and denosumab, which reduce bone resorption, or anabolic drugs such as teriparatide which increase bone formation. As these treatments may not be effective, other options are being studied.

One area of research has been a substance called sclerostin, which is produced by osteocytes. Its effect is to increase bone resorption and decrease bone formation. Bone density may therefore increase if the effects of sclerostin can be blocked.

Romosozumab is a monoclonal antibody that binds to sclerostin and inhibits its action. The drug has to be given by monthly subcutaneous injections. A practical consideration for patients is that the available formulation contains half the recommended monthly dose (210 mg). This means that two injections will be required. It takes about three months to reach a steady-state concentration. Like other antibodies, romosozumab is thought to be cleared by catabolism.

The ability of romosozumab to prevent vertebral fractures was studied in the FRAME trial. This enrolled postmenopausal women with reduced bone mineral density. One group of 3589 women received monthly injections of romosozumab while another group of 3591 women received placebo. After one year all the women were given injections of denosumab every six months for a further year. Bone density increased with romosozumab and the changes from baseline in the lumbar spine and hip were greater than in the placebo group throughout the trial. In the first 12 months of the trial, 1.8% of the women in the placebo group had a new vertebral fracture compared with 0.5% of the romosozumab group. The corresponding results at 24 months were 2.5% and 0.6%.[1]

Romosozumab was compared with oral alendronate in 4093 postmenopausal women, with low bone mineral density and a history of fractures, in the ARCH trial. After one year of treatment, the 2046 women randomised to receive romosozumab switched to alendronate. These women had greater increases in bone density than those who had only taken alendronate throughout the trial. Over 24 months, 6.2% of the women treated with romosozumab had a new vertebral fracture compared with 11.9% of the alendronate group. Non-vertebral fractures occurred in 8.7% of the romosozumab group and 10.6% of the alendronate group.[2]

Women who have not had a good response to bisphosphonates may be switched to an anabolic drug. The STRUCTURE trial compared the outcomes of switching to teriparatide or romosozumab. The 436 women in the trial had taken alendronate in the previous year and had used bisphosphonates for postmenopausal osteoporosis for at least three years. They also had a history of low bone mineral density and fracture. After 12 months, bone density at the hip had increased by 2.6% in the 218 women randomised to romosozumab compared with a decrease of 0.6% with teriparatide.[3]

Osteoporosis can also occur in men. The BRIDGE trial investigated whether romosozumab has an effect in men with low bone mineral density and a history of fracture. In this trial, 163 men received romosozumab and 82 men were given injections of placebo for 12 months. Bone density in the lumbar spine increased by 12.1% with romosozumab and by 1.2% with placebo. The corresponding changes at the hip were 2.5% and −0.5%.[4]

Common adverse events in the trials included arthralgia, muscle spasms and headache. Injection-site reactions were more frequent with romosozumab than with placebo.[1,4] Hypersensitivity reactions can occur. Approximately 18% of patients develop antibodies to romosozumab including 4.7% who develop neutralising antibodies. As osteonecrosis of the jaw has been reported, patients should have a dental examination before starting romosozumab.

During the ARCH[2] and BRIDGE[4] trials there were increases in serious cardiovascular adverse events with romosozumab. In the first year of the ARCH trial 2.5% of the women had serious events, including death, compared with 1.9% of the alendronate group.[2] Among the men taking romosozumab in the BRIDGE trial 4.9% had a serious event compared with 2.5% of the placebo group.[4] A possible explanation is that sclerostin could have a role in vascular calcification. Whatever the mechanism, romosozumab should not be used in patients who have had a stroke or myocardial infarction in the previous year.

While romosozumab was more effective than placebo at reducing the incidence of vertebral fractures in postmenopausal women with low bone mineral density, the difference in non-vertebral fractures did not reach statistical significance.[1] For women who have had a fracture, romosozumab appears to have an advantage over alendronate for preventing future fractures.[2] Whether the greater improvement in bone density, compared to teriparatide, in women switching

Some of the views expressed in the following notes on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

NEW DRUGS

from bisphosphonates results in fewer fractures remains to be seen.[3] As denosumab is often used when bisphosphonates are unsuitable, a comparative trial between denosumab and romosozumab would have been useful. As the effect of romosozumab subsequently declines, the drug should be stopped after 12 months.

T manufacturer provided the AusPAR

REFERENCES

1. Cosman F, Crittenden DB, Adachi JD, Binkley N, Czerwinski E, Ferrari S, et al. Romosozumab treatment in postmenopausal women with osteoporosis. N Engl J Med 2016 20;375:1532-43. https://doi.org/10.1056/NEJMoa1607948
2. Saag KG, Petersen J, Brandi ML, Karaplis AC, Lorentzon M, Thomas T, et al. Romosozumab or alendronate for fracture prevention in women with osteoporosis. N Engl J Med 2017;377:1417-27. https://doi.org/10.1056/nejmoa1708322
3. Langdahl BL, Libanati C, Crittenden DB, Bolognese MA, Brown JP, Daizadeh NS, et al. Romosozumab (sclerostin monoclonal antibody) versus teriparatide in postmenopausal women with osteoporosis transitioning from oral bisphosphonate therapy: a randomised, open-label, phase 3 trial. Lancet. 2017;390:1585-94. https://doi.org/10.1016/s0140-6736(17)31613-6
4. Lewiecki EM, Blicharski T, Goemaere S, Lippuner K, Meisner PD, Miller PD, et al. A phase III randomized placebo-controlled trial to evaluate efficacy and safety of romosozumab in men with osteoporosis. J Clin Endocrinol Metab 2018;103:3183-93. https://doi.org/10.1210/jc.2017-02163

The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, the European Medicines Agency and the Therapeutic Goods Administration.