New and emerging therapies for osteoporosis

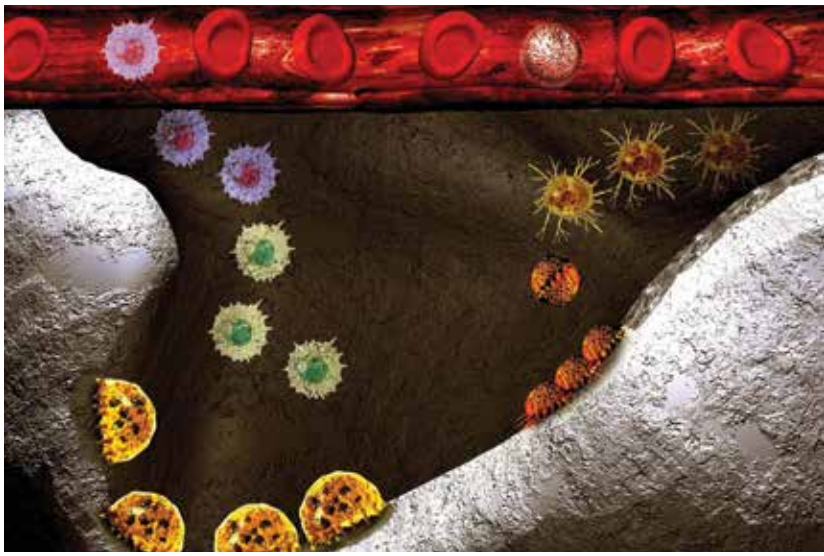
MELISSA CLARKE BPhty, MB BS(Hons I), FRACP
THOMAS DOVER BScApp(HMS), BHSc(Nutrition), MB BS, FRACP
EMMA DUNCAN MB BS(Hons I), FRCP, FRACP, PhD, LMusA

New medications for osteoporosis have broadened individualised treatment according to patient preference and specific clinical concerns. Sophisticated options for using new agents include combined or sequential prescribing, although PBS restrictions only allow suboptimal use of some agents.

Osteoporosis is a serious condition that is increasingly prevalent owing to Australia's ageing population. In 2012, osteoporosis and osteopenia affected 4.74 million or 66% of people in Australia aged over 50 years, resulting in 140,822 fractures. It is estimated that by 2022 this figure will increase by 31% and 6.2 million people aged over 50 will be affected.[1]

The considerable morbidity associated with fracture is readily appreciated by patients and doctors, and includes pain, anxiety, depression, loss of mobility and independence, and need for residential care. However, the increased mortality from osteoporotic fractures is much less appreciated. Hip fracture is associated with a five- to eightfold increased mortality within the first three months, with increased mortality continuing for 10 years.[2,3] Vertebral fractures and other major fractures are also associated with increased mortality.[4,5] Despite these worrying statistics, osteoporosis is often under-recognised: fewer than 20% of patients with minimal-trauma fractures are investigated or treated.[6]

'Traditional' osteoporosis medications have proven antifracture efficacy; however, they have some limitations. The most widely used are bisphosphonates. Oral bisphosphonates (alendronate and risedronate) can have gastrointestinal side effects, and the extremely rare risks of osteonecrosis of the jaw (1/10,000 to 1/100,000 patient treatment years) and atypical femoral fractures (1.8/100,000 per year with up to two years' exposure and 113/100,000 per year with 8 to 9.9 years' exposure) have caused some perhaps unjustified angst.[7,8] Menopausal hormone therapy



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Key points

- **Osteoporosis is a common yet under-recognised condition, with high morbidity and mortality.**
- **'Traditional' antiresorptive medications such as bisphosphonates, hormone replacement therapy and raloxifene are effective but have some limitations.**
- **Denosumab, a newer antiresorptive, has antifracture efficacy, and favourable 10-year safety data. It has generally similar side effects to bisphosphonates; however, hypocalcaemia is a potential risk particularly in people with stage 4 to 5 chronic kidney disease, and rebound-associated vertebral fractures have been observed after denosumab discontinuation. The role of denosumab in glucocorticoid-induced osteoporosis is under investigation.**
- **Teriparatide, the only available anabolic agent in Australia, is limited to 18 months' use. After discontinuation, commencement of an antiresorptive agent is strongly recommended.**
- **Combining denosumab and teriparatide appears promising, with impressive gains in bone mineral density; however, no fracture data are available yet, and the combination is not currently available on the PBS.**
- **Novel anabolic agents with phase III trial evidence include abaloparatide (a parathyroid hormone-related protein analogue) and romosozumab (an antisclerostin antibody).**
- **Although associated with significant fracture reduction in phase III trials, development of odanacatib (a cathepsin K inhibitor) has been discontinued because of a small increased risk of stroke.**

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Dr Clarke is an Endocrinology Registrar in the Department of Endocrinology and Diabetes at Royal Brisbane and Women's Hospital, Brisbane; and a Registrar–Associate Lecturer in the Faculty of Medicine, The University of Queensland, Brisbane. Dr Dover is a Senior Lecturer in the Faculty of Medicine, The University of Queensland, Brisbane; an Endocrinologist in the Department of Endocrinology and Diabetes, Mater Hospital, Brisbane; and an Endocrinologist in the Department of Endocrinology and Diabetes, Ipswich Hospital, Ipswich. Professor Duncan is an Eminent Senior Staff Specialist and Endocrinologist in the Department of Endocrinology and Diabetes, Royal Brisbane and Women's Hospital, Brisbane; Professor of Medicine in the Faculty of Medicine, The University of Queensland, Brisbane; and Adjunct Professor in the Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Qld.

has antifracture efficacy but may increase venous thromboembolism and stroke in all age groups and cardiovascular disease and breast cancer in women more than 10 years after menopause.[9-12] Raloxifene, a selective oestrogen receptor modulator, reduces vertebral fractures and breast cancer but does not prevent nonvertebral fractures, and increases venous thromboembolism.[9,13-15] Strontium ranelate is also contraindicated if the patient has a history of venous thromboembolism or vascular disease; it was removed from the PBS on 1 August 2016. Moreover, all these agents are antiresorptive rather than anabolic or 'bone-building'.

There are, however, several exciting new and emerging treatment options for osteoporosis, including several anabolic agents. These new medications are discussed in this article.

Denosumab

Denosumab is a human monoclonal antibody that binds the osteoblast-secreted cytokine receptor activator of nuclear factor κB ligand (RANKL), preventing it from activating the RANK receptor on osteoclasts, decreasing osteoclast development and activity and reducing bone resorption.[16] Denosumab is TGA approved and is given six-monthly as a 60 mg subcutaneous injection, with streamlined PBS authority for the indications of:

- a BMD T-score of -2.5 or lower in individuals aged 70 years or over
- fracture due to minimal trauma.

In the FREEDOM trial (Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months), compared with placebo, denosumab was associated with reductions in new vertebral, hip and nonvertebral fractures by 68%, 40%, and 20%, respectively.[16] Generally, denosumab is well tolerated and its use is supported by 10 years of favourable long-term safety data.[17] There have been case reports of osteonecrosis of the jaw and of atypical femoral fractures associated with denosumab.[18,19] Also, although cleared by the reticuloendothelial system, denosumab must be used cautiously in patients with stage 4 to 5 chronic kidney disease because of the risk of hypocalcaemia.[20] The role of denosumab in glucocorticoid-induced osteoporosis is under investigation.

Two recent publications compared denosumab with bisphosphonates. A one-year cohort study found similar rates of serious infection, cardiovascular disease and osteoporotic fracture in patients aged 50 years and over taking denosumab compared with zoledronic acid.[21] In a one-year randomised controlled trial (RCT) of postmenopausal women previously treated with oral bisphosphonates, denosumab was associated with greater bone mineral density (BMD) gains and greater inhibition of bone turnover than zoledronic acid.[22]

Discontinuation of denosumab results in increased bone turnover and a rapid loss of BMD back to baseline. There have been several reports of multiple vertebral fractures ('rebound-associated vertebral fractures') occurring shortly after treatment cessation.[23-28] Unlike nitrogen-containing bisphosphonates (e.g. risedronate, alendronate, zoledronic acid), denosumab does not cause osteoclast apoptosis; rather, bone biopsies show suspended osteoclasts and osteoclast precursors. It is hypothesised that once the suspended cells are released from the antiresorptive effect of denosumab, their simultaneous maturation results in activation of multiple bone-remodelling units and rapid bone resorption.[26] Alternatively, clearance of denosumab may result in an elevated RANKL–osteoprotegerin ratio, which similarly favours excessive resorption.[29] However, an evaluation of subjects in the FREEDOM trial who discontinued treatment after receiving two to five doses of denosumab or placebo and continued study participation for seven months or more showed no difference in fracture occurrence between the placebo and treatment groups, although this comparison did not adjust for BMD at the time of denosumab discontinuation.[30]

Nevertheless, given the potential rebound effect after discontinuation, some authors specifically advocate against 'drug holidays' from denosumab.[29] In general, the concept of drug holidays from antiresorptive agents is contentious; this should only be considered on a case-by-case basis for patients taking the longer-acting bisphosphonates alendronate and zoledronic acid. Even in these patients, the small risk of side effects needs to be weighed against the much larger risk of osteoporotic fracture, and recent data regarding atypical femoral fractures and long-term bisphosphonate therapy have been reassuring.[31] We do not favour drug holidays from denosumab, given its mode of action and the evidence for long-term safety and fracture protection; if denosumab is discontinued, use of a bisphosphonate should be considered to prevent rapid bone loss and rebound-associated fractures.

Teriparatide

The recombinant and shortened version of human parathyroid hormone (PTH), teriparatide (PTH 1-34), is the only anabolic agent currently available in Australia. Sustained PTH activation (as in primary hyperparathyroidism) predominantly results in bone loss; paradoxically, intermittent PTH activation (as in teriparatide administration) predominantly results in increase in bone mass.[32] PTH increases the RANKL–osteoprotegerin ratio, which increases osteoclast recruitment and activity, leading to resorption. Coupling of osteoblasts and osteoclasts results in upregulation of osteoblast activity also. Additionally, PTH decreases expression of *SOST* (the gene for sclerostin) in osteocytes, leading to activation of the anabolic Wnt signalling pathway (this pathway is discussed further below).[33]

In a landmark RCT that stopped at 17.5 months, 20 μg daily subcutaneous teriparatide reduced new vertebral fractures (14% with placebo *vs* 5% with teriparatide) and new nonvertebral fractures (6% *vs* 3% respectively) and was generally well tolerated (side effects included mild injection site reactions and mild transient hypercalcaemia).[34] The trial was stopped early because of new data showing an increased risk of osteosarcoma with teriparatide use in rats.[35] Unlike in humans, epiphyses (growth plates) do not fuse in rats, which may predispose them to osteosarcoma. Increased osteosarcoma rates have not been observed in humans; however, teriparatide is contraindicated in patients with prior skeletal irradiation, Paget's disease of bone and elevated alkaline phosphatase of unknown cause, and in individuals

with unfused epiphyses (i.e. children and adolescents).[6]

Similar to denosumab, teriparatide has 'off' effects after discontinuation, with loss of accrued BMD, although rebound fractures have not been observed. Thus, most bone physicians would start an antiresorptive agent on cessation of teriparatide. In the Denosumab and Teriparatide Administration (DATA)-Switch study, switching from teriparatide to denosumab increased BMD further; in contrast, switching from denosumab to teriparatide reduced BMD towards baseline.[36] The DATA-Switch authors suggested that the benefit of switching from teriparatide to denosumab may be due to rapid suppression of bone resorption by denosumab; although secondary suppression of bone formation will occur due to coupling, a short 'anabolic window' may favour increased bone mass.[36]

Teriparatide is TGA approved and can be prescribed under PBS authority for patients at very high risk of fracture who have a T-score of -3.0 or lower, have had two or more fractures due to minimal trauma, and have one or more symptomatic new fractures after 12 months or more of continuous antiresorptive therapy. Teriparatide must be initiated by a specialist or consultant physician but can be continued by general practitioners. The recommended dose is 20 µg daily, administered as a once-daily subcutaneous injection into the thigh or abdomen. Its use is limited to 18 months and commencement of an antiresorptive agent is strongly recommended after discontinuation.

A regimen of teriparatide once weekly has been shown to be effective in preventing vertebral fracture and improving BMD at teriparatide doses of 56.5 µg and 28.2 µg.[37,38] No comparison of the efficacy of weekly versus daily dosing has been published, and the treatment option of weekly dosing is not currently available in Australia.

Teriparatide combination therapy

The combination of teriparatide with antiresorptive therapies in postmenopausal women with osteoporosis has also been studied.

- In the DATA Extension study, two years of teriparatide plus denosumab significantly increased lumbar spine, femoral neck and total hip BMD more than either therapy alone, mostly within the first year.[39] Furthermore, teriparatide plus denosumab synergistically improved bone microarchitecture and estimated strength, particularly in cortical bone.[40]
- A one-year RCT showed menopausal hormone therapy combined with teriparatide increased BMD significantly more than menopausal hormone therapy alone (the combination was not compared with teriparatide alone).[41]
- A six-month RCT comparing teriparatide plus raloxifene versus teriparatide plus placebo found that combination therapy increased bone formation to a similar degree to teriparatide alone but with less bone resorption and greater total hip BMD gains.[42]
- A one-year RCT measuring lumbar spine and total hip BMD and comparing patients using zoledronic acid plus teriparatide with those using either agent alone showed the combination to be superior to either agent alone at early time points (≤26 weeks). However, at one year both combination therapy and teriparatide alone were superior to zoledronic acid alone regarding BMD at the lumbar spine, with no significant difference between combination therapy and teriparatide efficacy; conversely, combination therapy and zoledronic acid alone were both superior to teriparatide in terms of BMD at the hip, with no significant difference between the combination therapy and zoledronic acid alone.[43]

- The addition of alendronate to teriparatide has shown synergistic effects on BMD for total hip and lumbar spine in some studies but not others, with one earlier study of alendronate and teriparatide demonstrating greater increases in lumbar spine and hip BMD with teriparatide alone than with combination therapy.[44,45]

Overall, combination therapy with teriparatide is promising but, importantly, whether concomitant antifracture efficacy is improved requires evaluation. Ironically, the current PBS requirement of restricting teriparatide to patients who have already had at least 12 months of antiresorptive treatment is the least useful combination.[45-48] We would highlight that teriparatide combination therapy is not subsidised on the PBS.

Abaloparatide

Abaloparatide is an analogue of parathyroid hormone-related protein (PTHrP) 1-34, with modest structural homology with teriparatide (PTH 1-34) and similar anabolic effects on bone.[49] It is currently in phase III trials, and not TGA approved. The ACTIVE (Abaloparatide Comparator Trial in Vertebral Endpoints) study showed that subcutaneous abaloparatide 80 µg daily in postmenopausal women significantly reduced new vertebral and nonvertebral fractures over 18 months compared with placebo, and with significantly less hypercalcaemia compared with teriparatide 20 µg daily. The side effects were mild and included nausea, dizziness, headache and palpitations. The study was not powered to compare the effect on fracture reduction of abaloparatide compared with teriparatide, although abaloparatide was associated with significantly greater BMD gains at the lumbar spine at six and 12 months, but not at 18 months.[50]

The differential effects of abaloparatide and teriparatide may be explained by differential binding at the PTH receptor (PTH1R). Both PTH and PTHrP activate PTH1R, which has two different conformations, R^0 and RG.[49] Ligand binding to the R^0 conformation results in more prolonged duration of signalling compared with binding to the RG state.[51,52] Both teriparatide and abaloparatide bind with similar affinity to the RG conformation. However, abaloparatide has much less affinity for the R^0 conformation compared with teriparatide. Thus abaloparatide has relative selectivity for the RG state and more transient cell signalling responses compared with teriparatide, which may translate into differential effects on bone (anabolic and/or otherwise).[53]

Romosozumab

Sclerostin is an osteocyte-secreted protein that inhibits Wnt signalling in bone, resulting in reduced osteoblast-mediated bone formation.[54,55] Mutations in *SOST* cause excessive bone formation, demonstrated by bone dysplasias (sclerosteosis and van Buchem disease).[56] Based on these observations, romosozumab, a monoclonal antisclerostin antibody that increases bone formation, was developed.[57]

In a phase II study, romosozumab was evaluated over 12 months in postmenopausal women who had lumbar spine, total hip or femoral neck T-scores of between -2.0 and -3.5.[58] Monthly romosozumab 210 mg was associated with an 11.3% increase in lumbar spine BMD, compared with a decrease of 0.1% with placebo and increases of 4.1% with alendronate and 7.1% with teriparatide. Romosozumab was also associated with increased hip BMD, transient increases in bone formation markers and sustained decreases in bone resorption markers.[58] Romosozumab has also been shown to improve bone microarchitecture at multiple sites compared with placebo and teriparatide.[57]

The recently published phase III Fracture Study in Postmenopausal Women with Osteoporosis (FRAME) RCT assigned postmenopausal women who had total hip or femoral neck T-scores of between -2.5 and -3.5 to 12 months of romosozumab or placebo, followed by 12 months of denosumab. After 12 months there was a 73% relative risk reduction (RRR) in new vertebral fractures and a 36% RRR in clinical fractures in the romosozumab group (the absolute risk reduction was not reported). Nonvertebral fractures were not significantly reduced. Injection site reactions were slightly increased with romosozumab. There was one atypical femoral fracture associated with romosozumab, and two cases of osteonecrosis of the jaw (one after 12 months of romosozumab, the other after 12 months of romosozumab and one dose of denosumab).[59] Romosozumab is not TGA approved.

Odanacatib

Cathepsin K is an osteoclast-produced protease that degrades type I collagen and other bone matrix proteins.[60] Congenital absence of cathepsin K causes a high bone mass dysplasia (pycnodysostosis).[61]

In a phase II study, odanacatib, a selective cathepsin K inhibitor, was associated with a progressive increase in BMD over five years; bone turnover markers suggested reduced bone resorption but preservation of bone formation.[62] The phase III Long-Term Odanacatib Fracture Trial (LOFT) showed a 47% RRR in clinical hip fractures ($p<0.001$) and a 72% RRR in clinical vertebral fractures ($p<0.001$) in postmenopausal women.[63] However, odanacatib development has reently been discontinued because of the finding of a small increased risk of stroke (1.1% with placebo *vs* 1.4% with odanacatib).[64]

Conclusion

Osteoporosis is a common and serious health issue in Australia. In addition to existing efficacious therapies, there are several new agents either available (derosumab and teriparatide) or in advanced development (abaloparatide and romosozumab). Of these, teriparatide, abaloparatide and romosozumab are anabolic drugs. There are increasing data regarding more sophisticated use of these medications, such as combined or sequential prescribing. Disappointingly, current PBS restrictions only allow suboptimal use of some agents, particularly teriparatide. However, osteoporosis treatment can be individualised according to patient preference and specific clinical concerns, and the options are certain to improve in the future. **ET**

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A list of references is included in the website version of this article (www.endocrinologytoday.com.au).

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MELISSA CLARKE BPhty, MB BS(Hons I), FRACP; **THOMAS DOVER** BScApp(HMS), BHSc(Nutrition), MB BS, FRACP
EMMA DUNCAN MB BS(Hons I), FRCP, FRACP, PhD, LMusA

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