Rethinking osteoporosis

Long-term treatment strategy and sequential therapy

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Osteoporosis is a common chronic condition that can be managed to prevent disabling fractures. The number of available treatments is increasing, in particular new therapies with anabolic effects on bone as well as antiresorptive therapies. There is emerging but incomplete evidence that the choice of drug, duration and sequence of treatment needs to be tailored across the disease course for maximum benefit.

In healthy bone, the process of bone resorption by osteoclasts and bone formation by osteoblasts is tightly balanced. Osteocytes, previously described as senescent cells trapped within Haversian systems of non-remodelling bone, are now recognised as having an important regulatory role in the secretion of sclerostin (an inhibitor of bone mineralisation) and sensing of mechanical stress. Uncoupling of the processes of bone resorption and bone formation may result in increased bone fragility and increased fracture risk (osteoporosis).

Options for treatment and prevention of osteoporosis include lifestyle measures and a range of antiresorptive and anabolic medications. The number of medications that may be used is increasing rapidly. Osteoporosis is a chronic disease that progresses over the lifetime of the patient and therapies are often required indefinitely. Optimal strategies and sequencing of therapies may be required in some patients who continue to experience fractures or are at risk of potential drug-related adverse effects.

This article provides an overview of the current medication options to treat osteoporosis and recommendations on their use for fracture prevention as part of a long-term treatment strategy.

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Medications to treat osteoporosis in Australia

Available medications to treat osteoporosis include antiresorptive and anabolic therapies. The mechanisms of action of individual medications are shown in Figure 1 and summarised in Figure 2.

Antiresorptive medications target osteoclasts by various mechanisms to slow bone resorption and tip the balance in favour of bone formation. Bisphosphonates are analogues of inorganic phosphate; these attach to the hydroxyapatite binding sites of actively remodelling bone and prevent breakdown

KEY POINTS

- Antiresorptive drugs are the first-line treatment for mild osteoporosis, but there are important prescribing considerations.
- PBS and TGA criteria for use of antiresorptive and anabolic drugs vary widely between agents.
- Short courses of the anabolic treatment teriparatide are available for patients with severe osteoporosis but are underutilised; they should be used in sequence with other treatments.
- Other anabolic agents have undergone phase 3 studies but have not yet been approved by the TGA for use in Australia.

by osteoclasts.[1] Denosumab prevents bone resorption by acting as an antibody to receptor activator of nuclear factor kappa-B ligand (RANKL), which is essential for formation and survival of osteoclasts. Both the bisphosphonates and denosumab reduce bone turnover, retarding bone loss and reducing levels of biological markers of bone resorption (telopeptides of type 1 collagen and deoxypyridionoline). The long-term sequelae of a low-turnover state may include the rare adverse events jaw osteonecrosis and atypical femoral fractures.

Oestrogen replacement therapy, selective oestrogen receptor modulators (SERMs) such as raloxifene, and synthetic sex steroid medications such as tibolone act on oestrogen receptors (types α and β) expressed in bone cells. The overall effect is downregulation of bone turnover through a decrease in osteoclast differentiation, as well as inhibition of cytokine release from osteoblasts.[2]

In severe osteoporosis, bone loss is accompanied by poor-quality microarchitecture of bone.[3] The deterioration of trabecular structures is not well captured by traditional methods of bone densitometry, such as dual-energy x-ray absorptiometry (DXA), and may be better appreciated by high-resolution peripheral quantitative CT. Anabolic therapies such as teriparatide act directly on osteoblasts to promote bone modelling and improve both bone density and quality. Patients treated with teriparatide have increased trabecular numbers and thickness, which is not seen with antiresorptive treatment.[4]

Medications currently available to treat or prevent osteoporosis in Australia are shown with their TGA- and PBS-approved indications in Table 1.[5] Notable exclusions from PBS funding for antiresorptive therapy include:

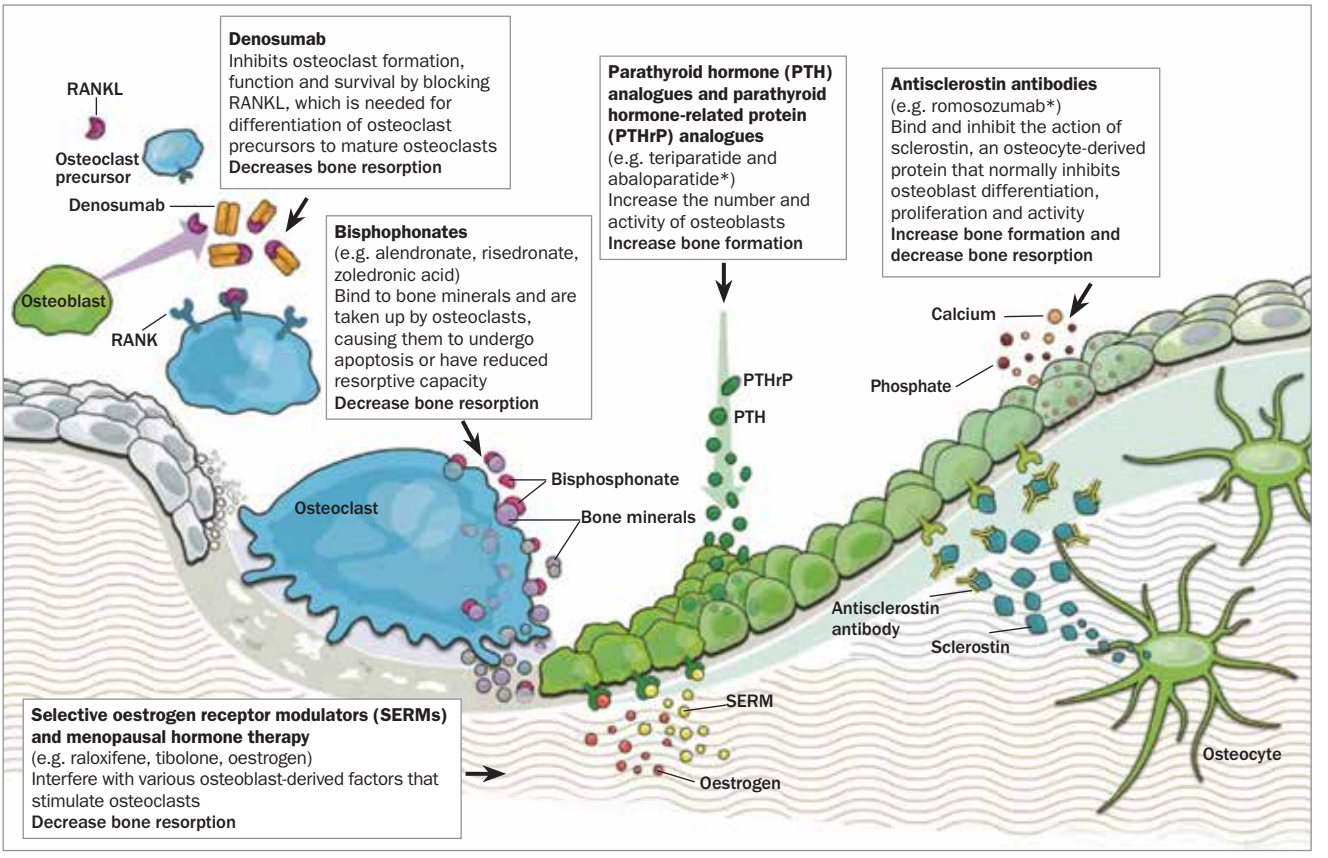


Figure 1. Mechanism of action of treatments for osteoporosis.

Abbreviations: RANK = receptor activator of nuclear factor kappa-B; RANKL = receptor activator of nuclear factor kappa-B ligand.

* Abaloparatide and romosozumab are not available in Australia.

Adapted with permission from Connelly D. Osteoporosis: moving beyond bisphosphonates (infographic). Pharmaceutical Journal 2016; 297: 23 Nov. doi: 10.1211/PJ.2016.20201978.

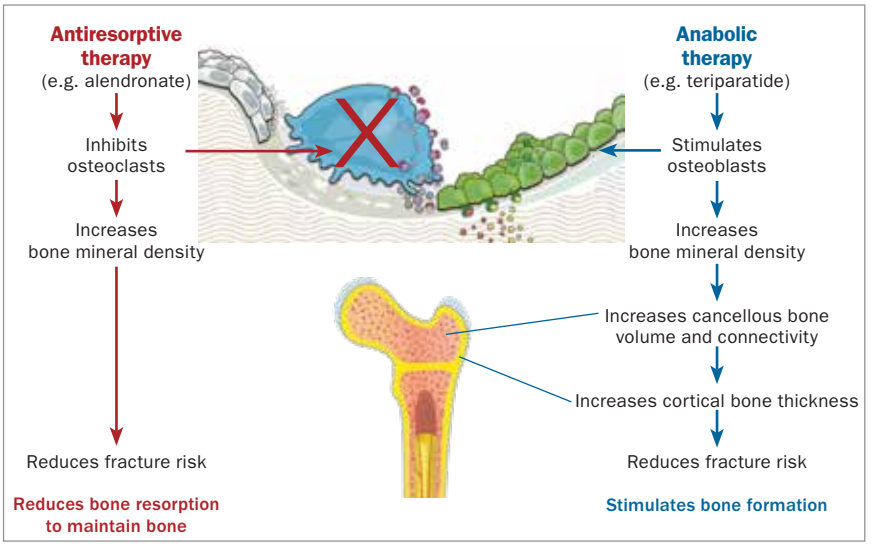


Figure 2. Comparison of mechanisms of action of antiresorptive and anabolic therapies for osteoporosis.

- people under the age of 70 years who have a T score in the established osteoporosis range (less than -2.5) but do not yet have a fracture
- people with hormone-responsive cancers who are being treated with long courses of antiandrogens or antioestrogens and those being treated with other drugs known to cause bone loss including antiretrovirals such as tenofovir.

It may be prudent for clinicians to discuss with these patients the option of self-funding antiresorptive therapy if their fracture risk is high (see FRAX and Garvan absolute risk calculators[6,7]) or bone loss is expected to be rapid.

Multiple preparations of menopausal hormone therapy are available on the general PBS schedule without a specific

TABLE 1. MEDICATIONS AVAILABLE TO TREAT OSTEOPOROSIS IN AUSTRALIA

Drug and formulations	PBS approved indications*	TGA approved indications[5]	Approximate cost (private)†
Antiresorptive therapies			
Alendronate (oral) 70 mg weekly	• Osteopenia, with T score ≤-1.5 and glucocorticoid use equivalent to prednisolone ≥7.5 mg/day for 3 months • Osteoporosis, with age ≥70 years and T score ≤-2.5 • Osteoporosis, with previous minimal trauma fracture	• Treatment of osteoporosis with T score ≤-2.0 • Treatment of osteoporosis with previous minimal trauma fracture	$10 per month = $120 per year
Risedronate (oral) 150 mg monthly, 35 mg weekly, 35 mg enteric coated weekly or 5 mg daily	• Preservation of bone density, with T score ≤-1.0 and glucocorticoid use equivalent to prednisolone ≥7.5 mg/day for at least 3 months • Osteoporosis, with age ≥70 years and T score ≤-2.5 • Osteoporosis, with previous minimal trauma fracture	• Treatment of osteoporosis • Treatment of glucocorticoid-induced osteoporosis • Preservation of BMD in patients on long-term corticosteroid therapy	$20 per month = $240 per year
Zoledronic acid (IV infusion) 5 mg annually	• Osteopenia, with T score ≤-1.5 and glucocorticoid use equivalent to prednisone ≥7.5mg/day for 3 months • Osteoporosis, with age ≥70 years and T score ≤-3.0 • Osteoporosis, with previous minimal trauma fracture	• Treatment of osteoporosis in postmenopausal women and patients aged ≥50 years with ≥1 low trauma hip fractures • To increase BMD in: – patients with osteoporosis associated with long-term glucocorticoid use – men with osteoporosis • To prevent glucocorticoid-induced BMD loss	$388 per 12-monthly infusion + infusion costs
Menopausal hormone therapy	• Not PBS listed for bone health	• Various	Various
Raloxifene (oral) 60 mg daily	• Osteoporosis in postmenopausal women with previous minimal trauma fracture	• Prevention and treatment of osteoporosis in postmenopausal women	$40 per month = $480 per year
Tibolone (oral) 2.5 mg daily	• Not PBS listed for bone health	• Second-line therapy for preventing BMD loss in postmenopausal women at high risk of osteoporotic fractures who cannot tolerate or are contraindicated for other products	$60 per month = $720 per year
Denosumab (SCI) 60 mg 6-monthly	• Osteoporosis, with age ≥70 years and T score ≤-2.5 • Established osteoporosis, with previous minimal trauma fracture	• Treatment of osteoporosis in – postmenopausal women – men at increased risk of hip fracture • Treatment to increase bone mass in men with osteopenia receiving androgen deprivation therapy for non-metastatic prostate cancer	$284 per 6 months = $568 per year
Anabolic therapies			
Teriparatide (SCI) 20 mcg daily for 18 months	• Osteoporosis, with – T score ≤-3.0 and – ≥2 minimal trauma fractures and – ≥1 minimal trauma fracture occurring despite 12 months of a first-line antiresorptive treatment (or intolerant of same) • Must be initiated by a specialist; continuing use can be prescribed by GPs	• Treatment of osteoporosis in postmenopausal women • Treatment of primary osteoporosis in men when other agents are considered unsuitable and they have a high risk of fractures • Treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in men and women at high risk of fracture	$432 per month = $5184 per year ($7776 for full 18-month course)

Abbreviations: BMD = bone mineral density; IV = intravenous; SCI = subcutaneous injection. * PBS approval is for monotherapy only for all drugs. Cost per prescription is $38.80 ($6.30 concession). † Prices advertised by a national pharmacy chain in December 2017 for patients wth a private prescription.

indication for osteoporosis treatment. These can be used for a short period for women who have recently reached menopause and have a low baseline risk of thromboembolic disease and breast cancer. Prescribing of menopausal hormone therapy for osteoporosis is an individualised decision that is discussed elsewhere.[8]

Tibolone is also TGA approved (but not PBS listed) as a second-line treatment for women with postmenopausal osteoporosis, when other agents are contraindicated or not tolerated.

Of note, PBS listing of strontium ranelate for treatment of osteoporosis was removed in 2016 because of a significantly increased risk of venous thromboembolism and cardiovascular events, and it is no longer manufactured.[9] It is recommended that patients taking strontium ranelate be transitioned to alternative agents.

Antiresorptive therapy

Efficacy of antiresorptive therapy in fracture reduction

It is well known that antiresorptive agents are underutilised for treatment of osteoporosis, in both primary and secondary fracture prevention. Hip fractures in older people can be catastrophic. Fewer than 10% of older Australians who experience a hip fracture are taking antiresorptive treatment for osteoporosis before the event, and only 16% are discharged from hospital with appropriate therapy initiated.[10] When follow up is extended to one year, still fewer than half of patients with a hip fracture will receive antiresorptive therapy.[11] Although fracture liaison services are being developed in Australia to capture patients with a fracture, primary care providers are well placed to recognise and address this issue.

Antiresorptive agents significantly reduce the risk of vertebral fractures and to a lesser degree hip and nonvertebral fractures. Each of the available antiresorptive agents has been well studied in comparison with placebo, and their antifracture efficacy is summarised in Table 2.[12-17] It is difficult to compare the effectiveness of these therapies directly as there is a paucity of head-to-head trials, and the placebo-controlled studies have involved different populations, illustrated by the variation in fracture rates between the placebo groups.

Adherence to oral bisphosphonate therapy is often incomplete. The antifracture efficacy of these medications correlates closely with dosing adherence.[18] This may explain the differences in results between trials and population-based observational studies. Denosumab has been compared with bisphosphonates in several clinical trials which showed superior increment in bone mineral density (BMD) but no demonstrable differences in fracture rates.[19] However, these trials were not sufficiently powered to detect a difference in fracture events.

Potential adverse effects of antiresorptive therapy

There are multiple considerations when prescribing antiresorptive therapies, to minimise the risk of adverse events.

Early adverse effects

Oral bisphosphonates can cause oesophageal ulceration or gastric irritation, particularly with non-enteric coated formulations. Patients who have difficulty swallowing or are unable to sit upright should not be prescribed oral bisphosphonates. Similarly, oesophageal dysmotility,

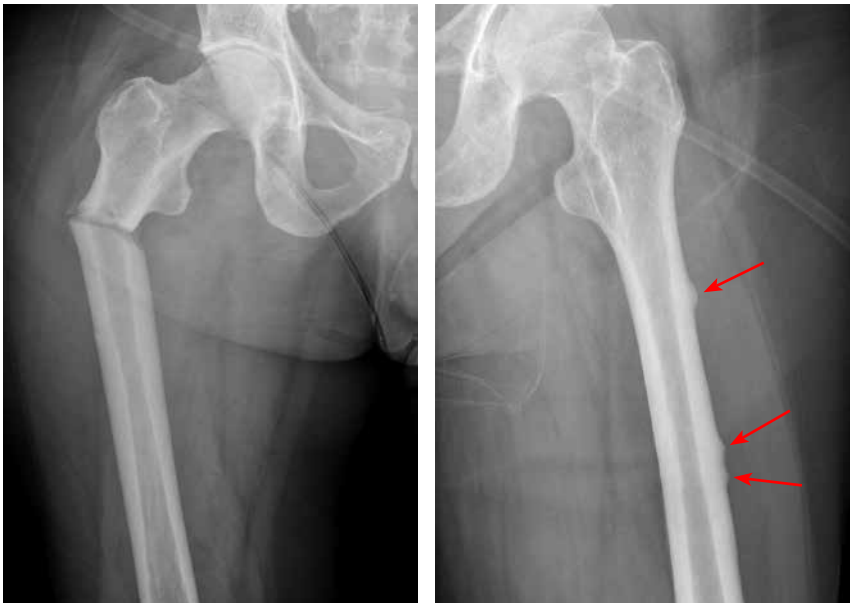
TABLE 2. ANTIFRACTURE EFFICACY OF ANTIRESORPTIVE AGENTS TO TREAT OSTEOPOROSIS[12-17]

Antiresorptive agent	Vertebral fractures			Nonvertebral fractures		
	Fracture rate		Relative risk (95% CI)	Fracture rate		Relative risk (95% CI)
	Intervention	Placebo		Intervention	Placebo	
Alendronate 5 to 10 mg daily for 3 years[12]	2.62%* 0.72%†	5.01%* 1.41%†	0.52 (0.42 to 0.66)	4.45%* 3.11%†	5.50%* 4.81%†	0.64 (0.51 to 0.80)
Risedronate 2.5 to 5 mg daily for 3 years[13]	11.3%	16.3%	0.59 (0.42 to 0.72)	5.2%	8.4%	0.61 (0.39 to 0.93)
Zoledronic acid 5 mg IV 12-monthly for 3 years[14]	3.3%	10.9%	0.3 (0.24 to 0.38)	8.0%	10.7%	0.75 (0.64 to 0.87)
Tibolone 1.25mg daily for 34 months[15]	3.1%	5.6%	0.55 (0.41 to 0.70)	5.4%	7.4%	0.74 (0.58 to 0.93)
Raloxifene 60 mg daily for 3 years[16]	6.6%	10.1%	0.7 (0.5 to 0.8)	8.5%	9.3%	0.9 (0.8 to 1.1), NS
Denosumab 60 mg 6-monthly for 3 years[17]	2.3%	7.2%	0.32 (0.26 to 0.41)	6.5%	8.0%	0.8 (0.67 to 0.95)

Abbreviation: NS = not significant. * Women with previous vertebral fracture. † Women with femoral BMD T score <-2.5.

ATYPICAL FEMORAL FRACTURES[25]

- Incidence is increased after five years of bisphosphonate use (incidence of up to 1 in 1000 patient years)
- Patient may have prodromal pain in thigh or groin
- Fractures occur spontaneously
- Typical x-ray appearance includes:
  - subtrochanteric or femoral shaft fracture
  - oblique or transverse fracture with medial cortical 'spike'
  - thickening of bony cortex
  - possible bilateral changes (up to 30%)
  - delayed healing
- Stop bisphosphonate and consider specialist referral for orthopaedic fixation and endocrinologist review



Figures 3a and b. Atypical femoral fracture. a (left). Right femur in a patient with a history of prolonged bisphosphonate exposure showing a complete transverse fracture through the femoral shaft (atypical femoral fracture). Note the generalised thickening of the cortical bone of the femoral shaft. b (right). Left femur of the same patient showing multiple sites of cortical beaking (arrows), which indicate a high risk of future atypical fractures in this bone.

strictures, previous Barrett's dysplasia, oesophagitis or active gastrointestinal reflux should prompt an alternative approach. Patients with abnormal gastric emptying or previous gastric bypass surgery may also experience issues.

Transient hypocalcaemia is a rare but concerning adverse effect of both denosumab and bisphosphonates, particularly intravenous formulations. It is more common in patients with pre-existing hypocalcaemia or hypoparathyroidism, vitamin D deficiency or renal impairment (stage 4 or 5 chronic kidney disease). Care should be taken to ensure adequate vitamin D levels (above 50 nmol/L) and normal serum calcium levels before dosing.

Zoledronic acid can result in a post-infusion inflammatory reaction, with flu-like symptoms, bone pain and myalgia within several days of the infusion. This reaction is usually mild to moderate in severity and decreases in frequency with subsequent doses (from 32% after the first dose, to 7% after the second dose and 3% after the third dose).[14] Oral bisphosphonates and denosumab may cause generalised myalgia or bone pain in approximately 3 to 6% of patients, which in rare cases can be disabling but improves after drug cessation.[20]

Other rare adverse effects of antiresorptive therapy include uveitis and inflammatory eye conditions with bisphosphonates, and local injection site reactions and skin infections with denosumab.

Longer-term adverse effects

Longer-term adverse effects of antiresorptive therapy include osteonecrosis of the jaw and, for bisphosphonates, atypical femoral fractures. Patients should be asked about their dental health, as any recent or upcoming invasive dental work (e.g. tooth extraction or a dental implant) increases the risk of osteonecrosis of the jaw. Active periodontal disease is a lesser risk factor. Osteonecrosis or prolonged exposure of the maxillary bone is caused by impaired remodelling by osteoclasts in the presence of bisphosphonate or denosumab. In patients taking these drugs to treat osteoporosis, the frequency of osteonecrosis of the jaw is between 0.01 and 0.04% but may reach as high as one in 300 in those undergoing dental extraction.[21] These rates dramatically increase with bisphosphonate or denosumab use in patients being treated for cancer.

Recent examination of the available long-term data shows that prolonged use of bisphosphonates increases the risk of atypical femoral fractures (Box and Figures 3a and b).[22-25] The increase in risk is seen particularly after five years of bisphosphonate use, but at its peak does not exceed one event per 1000 patient years.[26]

This observation has led to a recommendation that bisphosphonate use should be reviewed after five years for oral bisphosphonates and after three years for intravenous bisphosphonates.[22-24] It may be appropriate for patients with a previous major osteoporotic fracture or a BMD T score less than -2.5 to continue bisphosphonate therapy beyond this period, as these patients have the most favourable risk–benefit ratio. Patients who have a fracture while on bisphosphonate treatment are another high-risk group who should benefit from treatment extension

if escalation to anabolic therapies is not appropriate (see below). In these cases, oral bisphosphonates may be extended up to 10 years. In a retrospective population study in Denmark, long-term users of alendronate with high hip fracture incidence (10.9% over 6.9 years mean follow up) continued to benefit at 10 years of treatment, with 30% reduction in hip fracture incidence, without a detectable increase in atypical fractures.[27]

Other lower-risk patients may be considered for a treatment break; this is sometimes termed a 'drug holiday', but this is misleading as the reservoir of bisphosphonate within bone will result in some continued antifracture efficacy. Patients on a treatment break need to be reviewed following repeat bone densitometry after three years.

Adverse effects on treatment cessation

The long-term efficacy and safety of denosumab has been examined for up to 10 years of therapy.[28] Continuous improvement in BMD is seen with no plateau effect, with ongoing efficacy for fracture prevention. However, cessation of denosumab, unlike bisphosphonates, leads to rapid bone loss of 6 to 7% within one year.[29] There is a well described 'bone turnover rebound', where markers of bone resorption increase rapidly. For some individuals, this rebound is seen within a few months of the missed denosumab dose, emphasising the need for strict compliance with the six-monthly dosing interval. Case reports have emerged of women having multiple vertebral fractures shortly after denosumab cessation, as early as nine months after the last dose.[30] Consensus guidelines now suggest that denosumab should not be ceased without another osteoporosis agent being substituted, preferably an oral bisphosphonate, to prevent this rebound phenomenon.[31]

Monitoring of antiresorptive therapy

Patients with osteoporosis should be monitored regularly for treatment effect or failure, and any adverse events as outlined above. This may result in the need to escalate to second-line therapies, including anabolic agents.

In general, BMD can be monitored at 24-monthly intervals for patients on treatment. Care should be taken to refer for BMD measurement by the same method (DXA or, in specialised settings, quantitative CT) and preferably with the same provider to allow accurate detection of small changes over time and low precision error. Suboptimal response to an antiresorptive agent can be detected by a significant loss of bone density on serial measurements (more than 5% and 4% for spine and hip BMD, respectively) despite treatment adherence.[32] BMD providers should report on their 'least significant change', which allows a margin of measurement error between readings.

Specialists may use more frequent BMD measurements (after 12 months of treatment) or assessment of bone turnover markers. The latter can help to monitor treatment response or to decide when to reinitiate bisphosphonates after a treatment break. These approaches are used in individual cases, but no guidelines exist for routine use of bone turnover markers.

Patients on treatment should be reviewed earlier if they experience a further osteoporotic fracture or an atypical femoral fracture. Symptoms and signs that should raise suspicion include new midline back pain, worsening kyphosis or height loss; these should prompt evaluation for new vertebral fractures by x-ray or CT imaging. Minimal trauma fractures, which occur from standing height or less, should also alert to the need to review treatment. Persistent groin or thigh pain in patients treated long-term with a bisphosphonate or denosumab may herald an atypical femoral fracture.

Anabolic therapy

Efficacy of anabolic therapy in fracture reduction

Patients who have recurrent fractures despite antiresorptive therapy and those with severe osteoporosis (BMD T score less than -3.0) qualify under the PBS for anabolic (bone-building) therapy.

Currently in Australia, the only approved anabolic agent to treat osteoporosis is teriparatide, a recombinant form of parathyroid hormone (PTH) that is delivered via a daily subcutaneous injection from a multidose delivery device ('pen'). Teriparatide treatment leads to a significant increase in BMD, with an associated reduction in fracture risk.[33] Teriparatide has been directly compared with risedronate for treatment of postmenopausal osteoporosis and secondary prevention of vertebral fractures. Teriparatide treatment resulted in significantly fewer vertebral fractures and clinical fractures (Table 3).[33-37] In a cohort of older people who had experienced a hip fracture, a course of teriparatide was superior to risedronate for BMD gains, lower postfracture pain and better mobility (as measured by a timed rise from chair and walk).[38]

Teriparatide (like all anabolic agents) is used for a limited time only. In Australia, PBS funding of teriparatide is limited to 18 months, but it can be prescribed for up to 24 months in the USA and Europe. Long-term exposure is not permitted because of animal safety data suggesting increased rates of osteosarcoma in rats; this has not been borne out in observational data in humans with use up to 24 months.[39] Patients with known risk factors for osteosarcoma, including Paget's disease or previous bone irradiation, should not receive this medication.

About 3% of patients receiving teriparatide may require a dose reduction to second-daily injections because of transient hypercalcaemia after administration. It is important to check serum calcium level (before the daily dose) six weeks after initiation and three-monthly thereafter unless otherwise indicated. Apart from this, teriparatide is well tolerated, with a low incidence of nausea, dizziness and headache. Serum uric acid levels increase slightly in some patients and should be monitored in those with a clinical history

TABLE 3. ANTIFRACTURE EFFICACY OF ANABOLIC AGENTS TO TREAT OSTEOPOROSIS[33-37]

Anabolic agent versus comparator	Vertebral fracture			Clinical fracture		
	Fracture rate		Relative risk (95% CI)	Fracture rate		Relative risk (95% CI)
	Anabolic agent	Comparator		Anabolic agent	Comparator	
Teriparatide 20 mcg daily versus placebo for 21 months[33]	5%	14%	0.35 (0.22 to 0.55)	3%	6%	0.47 (0.25 to 0.88)
Teriparatide 20 mcg daily versus risedronate 35 mg weekly for 24 months[34]	5.4%	12.0%	0.44 (0.29 to 0.68)	4.8%	9.8%	0.48 (0.32 to 0.74)
Romosozumab 210 mg monthly versus placebo for 12 months, followed by denosumab 60 mg SCI six-monthly for 12 months[35]	0.6%	2.5%	0.25 (0.16 to 0.40)	2.8%	4.1%	0.67 (0.52 to 0.87)*
Romosozumab 210 mg monthly versus alendronate 70 mg weekly for 12 months, followed by alendronate 70 mg weekly for 12 months[36]	6.2%	11.9%	0.52 (40 to 0.66)	9.7%	13.0%	0.73 (0.61 to 0.88)
Abaloparatide 80 mcg daily versus placebo for 18 months, followed by alendronate 70 mg weekly for 6 months[37]	0.55%	4.4%	0.13 (0.04 to 0.41)	4.0%	7.1%	0.55 (0.33 to 0.92)

* Secondary endpoint, with nominal P value 0.002, adjusted P value 0.096 (not significant).

of gout. A recommended resource for prescribing teriparatide can be found at the website of the National Prescribing Service (https://www.nps.org.au/radar/articles/teriparatide-forteo-for-severe-osteoporosis#r8).

Other anabolic therapies for osteoporosis include romosozumab, a monoclonal antibody against sclerostin, an inhibitor of bone formation, and abaloparatide, a PTH-related protein analogue. Romosozumab has undergone phase 3 trials and showed superior antifracture efficacy in head-to-head comparison with alendronate alone in preventing fractures at all sites.[36] However, concerns have been raised about a slightly increased rate of cardiovascular events with romosozumab that will require additional evaluation before this drug is approved for use. Abaloparatide has been trialled against placebo and showed reductions in fracture risk at both vertebral and nonvertebral sites, exceeding the reductions seen in trials of antiresorptive agents (i.e. bisphosphonates, raloxifene and denosumab).[37]

Anabolic therapy as part of a sequential regimen

Anabolic therapies have short-lived but potent effects. As teriparatide is PBS-funded as a second-line monotherapy for osteoporosis with a short treatment duration, it is logical to consider its place in a sequence of therapies for osteoporosis.

Prior treatment with various antiresorptives may affect the BMD increases seen with anabolic therapy. There was no demonstrable difference in efficacy between patients who have used hormone therapy or raloxifene before teriparatide versus those who were untreated.[40] However, bisphosphonates administered shortly before teriparatide treatment appeared to attenuate the expected BMD gains during an 18-month course of treatment; the mean lumbar spine BMD improved by 10.2% in patients pretreated with raloxifene but by 4.1% in those pretreated with alendronate.[41] In patients pretreated with denosumab, a transient BMD decrease was seen after the switch to teriparatide.[42]

In contrast, combination regimens with teriparatide and another antiresorptive drug appear to achieve the greatest improvements in BMD (although these combinations are not PBS funded). Combined therapy with denosumab and teriparatide results in stronger BMD gains at the hip than either agent used in sequence.[42] Zoledronic acid in combination with teriparatide also gave stronger BMD gains than either agent used alone.[43] However, whether these stronger BMD gains translate to improved antifracture efficacy in these patients remains unclear. The effect of teriparatide is likely to be distinct from its effect on mineralising bone, which is the primary index measured on DXA, as bone formed following teriparatide treatment tends to be less mineralised.[44]

There is an apparent paradox between the funded indication for anabolic therapies and their most effective place in the sequence of osteoporosis therapy, which is upfront, before antiresorptive drugs. In fact, the use of teriparatide has been demonstrated as a safe and effective first-line treatment in individuals with

severe osteoporosis who do not meet the PBS criteria. This includes people aged over 65 years with T scores less than -2.5 or younger people with T scores less than -3.5. Teriparatide can also be used in patients with glucocorticoid-induced osteoporosis.[40] However, the cost on private prescription (more than $400 per month for 18 months) is prohibitive for many patients.

It is clear that after a course of anabolic therapies is completed, it should be followed by an antiresorptive drug. After teriparatide discontinuation, the reduced risk of fractures persists for 18 months. The untreated BMD reduces slowly, although it does not return to pre-treatment levels over 30 months of observation.[45] This slow reduction in BMD can be prevented by instead switching to a bisphosphonate or denosumab, leading to an even more prolonged period of antifracture efficacy and further BMD gains.[46,47]

When to refer patients with osteoporosis

Criteria for referring patients for specialist review include:

- intolerance of multiple osteoporosis treatments
- occurrence of atypical fracture, osteonecrosis of the jaw or another treatment complication
- further fracture on antiresorptive treatment
- consideration of anabolic therapy (must be specialist initiated).

An exemplary referral contains information about all previously prescribed osteoporosis treatments and duration of use.

Conclusion

Osteoporosis is common and affects patients over many years. It is helpful for GPs to be familiar with the options for first-line osteoporosis treatment, which patients might be suitable for each therapeutic option and for how long they should be used. Patients taking a bisphosphonate should be reviewed after three to five years of treatment. Denosumab should not be ceased without consideration of a short course (one to two years) of an oral bisphosphonate to prevent vertebral fractures. Anabolic therapies are often overlooked but have an important role in sequential therapy for severe osteoporosis and in people with recurrent fractures. MT

References

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

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