Ongoing osteoporosis management

Dealing with dilemmas

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Every patient being treated for osteoporosis should be reviewed periodically to ensure that therapy remains appropriate and that all aspects of care have been optimised.

Osteoporotic fracture is a major cause of morbidity and mortality in the Australian population despite the availability of treatment that is proven to substantially reduce fracture risk. Many of those at risk do not receive appropriate therapy. Nevertheless, there has been a steady rise in the uptake of appropriate therapies and, as people are living longer, issues have arisen about how best to manage those receiving treatment over long periods. These include:

- When should treatment be reviewed, suspended or changed?
- When has treatment failed?
- What are the risks of ongoing treatment?
- How can treatment be optimised?

These questions are discussed below. Three cases that illustrate some of the issues are outlined in Box 1 and the Table.

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How much antiosteoporotic therapy is enough?

Concerns about whether and when to consider suspending antiosteoporotic therapy are in part prompted by the rare complications of osteonecrosis of the jaw and atypical femoral fracture (AFF; discussed below). When considering whether to continue or to suspend or cease antiosteoporotic therapy, the risks and benefits of both courses of action should be assessed. As a baseline position, an elderly patient with a previous fracture is at substantial risk of having another fracture.

For patients taking a bisphosphonate, it has sometimes been considered that therapy can and should be ceased after five years, or that patients should take a 'drug holiday'. In a 2006 study in which patients taking alendronate for five years either continued or discontinued for a further five years, bone mineral density (BMD) showed a moderate decline in those ceasing therapy, with an increase in vertebral but not nonvertebral fractures compared with those who continued.[1] (Of note, over 40% of trial participants had a BMD T score of –2 or higher at enrolment, and only 60% had a previous fracture, so the trial participants may have had less severe osteoporosis than many patients in whom the question of continuing therapy arises.) Limited data exist regarding bisphosphonate use beyond five years, but it appears that vertebral fracture at least is reduced with longer-term therapy. The patients considered most likely to benefit from continued bisphosphonate use are those with a femoral neck T score lower than –2.5 and those with an existing vertebral fracture and a femoral neck T score lower than –2.0.[2]

A commonly recommended clinical approach is to consider suspending bisphosphonate therapy if:

- there has been no further fracture and
- the femoral neck T score has risen to the nonosteoporotic range (greater than –2.5).

1. CASE SCENARIOS OF THREE WOMEN RECEIVING OSTEOPOROSIS TREATMENT

Maureen

Maureen, aged 78 years, attends her GP at her family's request for a review regarding ceasing bisphosphonate therapy. She was prescribed alendronate at age 70 years following a wrist fracture. She has had no further fractures.

Other medical problems include generalised hypertension, previous gastric ulcer, glaucoma and osteoarthritis, particularly affecting the lumbar spine, knees and hips. Her other medications include calcium carbonate twice daily, esomeprazole, perindopril and glaucoma eye drops. She currently lives at home with her elderly husband, with no services required.

Her recent bone mineral density (BMD) test scores are shown in the Table. They are low but essentially unchanged compared with her scores before commencing therapy (current range –2.5 to –2.7). Her serum vitamin D level is 65 nmol/L on no replacement.

Kathleen

Kathleen, aged 74 years, attends her GP after discharge from a rehabilitation facility following a fracture of the femoral neck. She has chronic airflow limitation, mild dementia, hypertension, lumbar spine degenerative disease and diabetes.

Her osteoporosis history includes a fracture of the neck of the humerus at age 68 years from a simple fall, after which she was commenced on a weekly oral bisphosphonate, which she says she takes 'most of the time'. She is determined to live alone, continues to smoke, drinks alcohol infrequently and has a limited diet.

BMD testing shows a lumbar spine T score of –1.5 (previously –1.4 at age 68 years), total hip T score of –2.7 (previously –2.3) and femoral neck T score of –3.1 (previously –2.7). Her vitamin D level is suboptimal at 40 nmol/L.

Susan

Susan, aged 64 years, has had three doses of intravenous zoledronic acid, beginning at age 60 years after a radius fracture from minimal trauma. She has had no further fractures. She has improved her dietary calcium intake substantially over the interim, and her serum vitamin D level has remained around 70 nmol/L.

Her T scores have improved at the spine (–2.0 to –1.3), total hip (–1.6 to –1.2) and femoral neck (–1.9. to –1.5).

However, the individual's fracture risk should also be reviewed before deciding whether to discontinue therapy, taking into account features such as falls risk and family history.[3] Individual fracture risk calculators are available online (e.g. the FRAX and Garvan risk calculators discussed below). These are designed to aid decision-making regarding whether patients should commence therapy rather than whether they should continue therapy, but the listed risk factors can be useful reminders of contributors to ongoing risk, when judging whether therapy can safely be suspended.

Whether or not a drug holiday is necessary or beneficial remains controversial and unproven; a patient-based assessment of risk appears prudent.[4] The small risks of complications of therapy need to be balanced against the benefit conferred by ongoing therapy.

With this in mind, a younger patient such as Susan, whose baseline fracture risk was moderate, who has sustained no further fractures, and whose BMD has improved might be an appropriate candidate for a trial of treatment suspension. On the other hand, in an elderly patient such as Kathleen, with several previous fractures and a high risk of falls, the major benefit of continuing therapy is likely to outweigh the small risk of complications of therapy.

All patients should have their bone therapy reviewed periodically. If a drug holiday is decided on then patients should be monitored; the optimum duration of these holidays is not clear and is complicated by differences between anti-osteoporotic drugs. Bisphosphonates persist in bone for a number of years after discontinuation, with alendronate and zoledronic acid persisting longer than risedronate. In contrast, after discontinuation of denosumab, bone turnover markers increase and bone density decreases relatively rapidly but improves if treatment is recommenced.[5]

It has been broadly suggested that patients might be considered 'treatment naïve' around two years after stopping bisphosphonate therapy (taking into account differences between bisphosphonates). A decision about whether to recommence therapy could then be based on clinical criteria, perhaps including a fracture risk predictor such as the FRAX or Garvan fracture risk predictors (http://www.shef.ac.uk/FRAX and http://garvan.org.au/promotions/bone-fracture-risk/calculator).[6,7] These would usually be most appropriately used in patients who have not yet commenced therapy.

TABLE. BMD RESULTS FOR THREE WOMEN RECEIVING OSTEOPOROSIS TREATMENT

Patient	Age (years)	Current BMD T score (T score before treatment)*		
		Lumbar spine	Total hip	Femoral neck
Maureen	78	–2.6 (–2.5)	–2.5 (–2.5)	–2.7 (–2.8)
Kathleen	74	–1.5 (–1.4)	–2.7 (–2.3)	–3.1 (–2.7)
Susan	64	–1.3 (–2.0)	–1.2 (–1.6)	–1.5 (–1.9)

Abbreviation: BMD = bone mineral density. * T score = number of standard deviations below 'young-normal'.

2. CRITERIA FOR TREATMENT FAILURE IN OSTEOPOROSIS*

Osteoporosis treatment may be considered to have failed in the presence of:

- two or more new low trauma fractures
- one new low trauma fracture with either (or both) of
  - failure of suppression of bone turnover markers
  - a significant decline in BMD
- no new low trauma fracture but both
  - failure of suppression of bone turnover markers and
  - a significant decline in BMD

* Modified from Diez-Perez et al, 2010.[10]

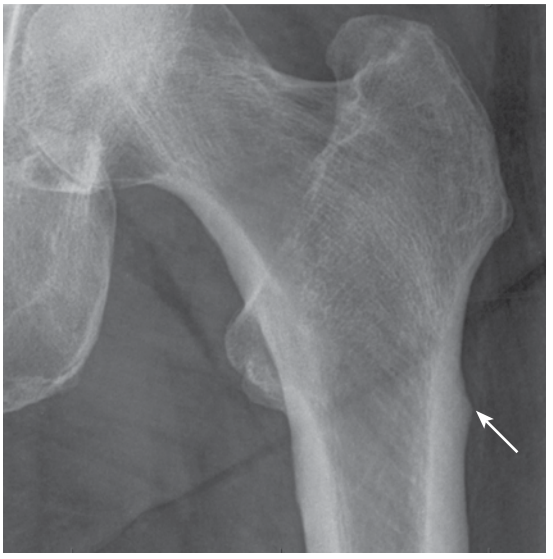

Figure 1. Early x-ray changes of an incomplete atypical femoral fracture in a patient who presented with new bilateral thigh pain after using bisphosphonates for longer than 10 years. The x-ray showed lateral cortical thickening in the proximal left femur (arrow). Findings in the right femur were similar. A subsequent bone scan (Figure 2) appeared consistent with bilateral incomplete atypical femoral fractures.

Image courtesy of Alfred Imaging, Newtown, NSW.

When should treatment be changed?

Patient adherence with prescribed oral bisphosphonates is generally quite poor. Suboptimal adherence has been shown to be associated with increasing fracture risk in a number of studies.[8] Antifracture efficacy declines steadily with decreasing compliance; patients taking bisphosphonates half the time appear to have only marginal benefit compared with those not taking the medication.[9]

If weekly oral bisphosphonates are not well tolerated or adherence is poor then options for treatment variation include those listed below.

- A change to a monthly formulation can be considered, although gastrointestinal intolerance may persist.
- Strontium ranelate has a limited role given recent data linking it with a possible increased risk of cardiac events in patients with existing heart disease or hypertension; it is reimbursable on the PBS only if no other agent can be used.
- Raloxifene lacks evidence of efficacy for reducing hip fracture risk, although there is evidence that it reduces vertebral fracture risk. It is not usually a first choice in older patients where the risk of hip fracture is of primary concern, but it may have a role in those whose risk of hip fracture is not high and in younger patients with low spinal BMD.
- Parenteral antiresorptive therapy, either six-monthly subcutaneous denosumab or annual (or less frequent) intravenous zoledronic acid, could be considered. For these parenteral drugs, it is important that vitamin D level be adequate (at least 50 nmol/L) before administration. No fracture data regarding the efficacy of switching therapies is available.
- In patients with very severe osteoporosis with repeated fractures despite adequate antiresorptive therapy, daily teriparatide injections may be indicated. These patients should be referred to a bone specialist.

When has treatment failed?

A new fracture does not necessarily indicate osteoporosis treatment failure. In assessing treatment, it should be remembered that bisphosphonates approximately halve the risk of future fracture but do not completely eliminate the risk. Treatment failure may be defined according to the criteria in Box 2.[10]

Bone turnover markers are not commonly assessed but may be useful in some circumstances to determine whether bone turnover is adequately suppressed (which could indicate lack of adherence or poor absorption of oral agents) or oversuppressed (when a drug holiday might be appropriate). Recommended bone turnover markers include:

- bone formation markers – bone-specific alkaline phosphatase and procollagen type 1 N-terminal propeptide (P1NP)
- bone resorption marker – C-terminal telopeptide of type 1 collagen.

If treatment is deemed to have failed then it is important to assess contributing factors, such as poor adherence, vitamin D deficiency, intercurrent illness, medications and lifestyle factors, including alcohol or tobacco use or lack of appropriate physical activity. A change of treatment should also be considered.

What are the risks of ongoing treatment?

Osteonecrosis of the jaw

Osteonecrosis of the jaw is a rare condition known to be associated with antiresorptive drugs, including bisphosphonates and denosumab. It is characterised by exposure of the bone surface with loss of overlying mucosa, pain and poor healing. The

3. CRITERIA FOR DIAGNOSING AN ATYPICAL FEMORAL FRACTURE*

An atypical fracture of the femoral shaft should be considered if:

- the fracture is located along the line of the femoral diaphysis from just distal to the lesser trochanter, to just above the supracondylar flare AND it fulfils
- major criteria (four out of five required)
  - minimal or low trauma
  - originates at lateral cortex and is predominantly transverse
  - complete fracture extend through both cortices and may have medial spike
  - no or minimal comminution
  - localised periosteal or endosteal thickening of lateral cortex at fracture site
- minor features (need not be present but may be associated)
  - generalised increased in femoral diaphysis cortical thickening
  - prodromal symptoms of aching pain in thigh or groin
  - bilateral complete or incomplete fractures
  - delayed fracture healing

* Modified from Shane et al.[13]

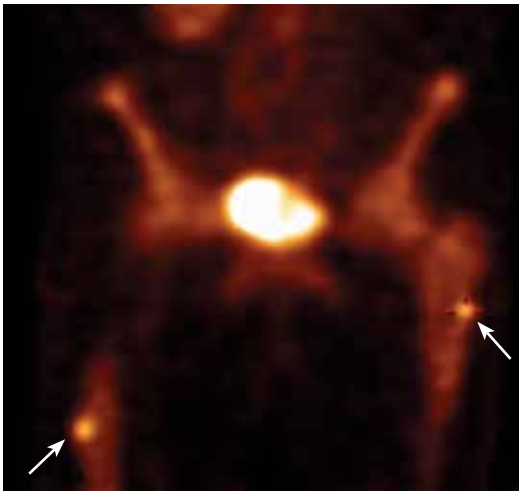

Figure 2. Nuclear bone scan using single photon emission computed tomography (SPECT) in the patient in Figure 1, showing bilateral incomplete atypical femoral fractures. Arrows indicate increased isotope uptake in the lateral cortex of the proximal and midshaft of the left femur and midshaft of the right femur, consistent with stress fractures.

Image courtesy of Alfred Nuclear Medicine and Ultrasound, Newtown, NSW.

condition can occur spontaneously but is more usual in the setting of major dental manipulation, such as tooth extraction or placing of an implant, or oral infection.

The association between osteonecrosis of the jaw and bisphosphonate use was first noted in oncology patients receiving frequent high bisphosphonate doses intravenously. In patients receiving bisphosphonates for osteoporosis, the risk of osteonecrosis of the jaw appears very low (one in 100,000 for oral bisphosphonates and less than one in 5000 for intravenous bisphosphonates). The risk for those receiving denosumab is difficult to quantify but also appears to be very low, perhaps of the order of oral bisphosphonate risk.

The risk of osteonecrosis of the jaw appears to be higher around the time of dental extraction. Additional risk factors seem to be older age, use of oral corticosteroids, diabetes, gum disease and smoking. The absolute risk of osteonecrosis of the jaw is exceedingly low. Whether measurement of bone turnover makers can help in establishing a 'safe' time for dental extraction is unclear.[11] Although it is common practice to suspend antiresorptive therapy at the time of extraction, this has not been proven to reduce risk, and most patients undergo dental work without any adverse effects. If significant dental work is forecast then most clinicians recommend that it be completed before starting antiresorptive therapy. It should be noted that not all jaw or tooth pain represents osteonecrosis of the jaw, and diagnosis requires dental or oromaxillary review.

Atypical femoral fracture

AFF is a relatively recently recognised phenomenon thought to be associated with generalised suppression of bone turnover and noted particularly in patients taking bisphosphonates.[11] AFFs typically occur in the midshaft of the femur. An x-ray may reveal lateral femur stress changes (Figure 1, Box 3). A bone scan can be diagnostic (Figure 2). Patients using bisphosphonates or denosumab for long periods appear to be at most risk; additional risk factors include corticosteroid use and possibly Asian background.[12]

The most important practical feature is that patients often present with weeks or months of nonspecific thigh pain, which may be a sign of the development of an incomplete or stress fracture. Early recognition may allow completion of the fracture to be avoided. Therefore, a history of thigh pain should be sought in any review of a patient treated with antiresorptive agents. Plain x-rays may not be sufficient to exclude this condition; a bone scan, CT or MRI imaging may be required. As the condition is bilateral in around a quarter of cases, the other side of the body should also undergo imaging, even if asymptomatic.[12]

The risk of this type of fracture is low: it is estimated at one in 1000 patients after eight years of oral bisphosphonate use and considered very rare in patients using denosumab.[12] Suspending the medication may reduce the risk. Incomplete and complete fractures both require specialist care (physician and orthopaedic). Completed fractures require pinning; incomplete fractures may sometimes be treated conservatively, and teriparatide therapy may have a role.[13]

Although AFFs are a serious type of fracture, they are rare. It should be remembered that the use of antiresorptive drugs reduces hip fracture risk by up to half. The drugs are far more likely to prevent a fracture than to cause one.

How can overall management be improved?

The recommended calcium intake for men and women aged over 70 years is 1300 mg, with three serves a day optimal.[14] This is often difficult to achieve from the diet alone in elderly patients. Given the current controversy surrounding the use of calcium supplements and the possible increased risk of myocardial ischaemic events, it is now recommended that dietary calcium is preferable to supplementation. Optimisation of dietary calcium intake should be encouraged in patients receiving antiosteoporotic therapy. If this seems unlikely or impossible, as in Kathleen's case because of her limited diet, then calcium supplementation should be considered. Calcium citrate may be better absorbed than calcium carbonate, particularly in patients taking proton pump inhibitors or H_2 blockers, as in Maureen's case.[15]

The ideal range for vitamin D is controversial, but authorities agree that the level should be at least 50 nmol/L year-round, as levels can vary with the seasons. A level of around 80 nmol/L may be more appropriate for frail elderly patients with osteoporosis who are at highest fracture risk, as low vitamin D levels are also associated with increased risk of falling. Measuring serum vitamin D when osteoporosis is diagnosed or suspected and then after an adequate period of replacement (several months), and thereafter considering annual measurement at the end of winter is sufficient. If tablets, capsules or drops are insufficient (remembering that a 1000 IU supplement can be expected to increase the serum level by about 10 to 20 nmol/L) then intermittent moderately high oral doses (50,000 IU) may be considered. (Some unexpected data have suggested that a very high annual dose of 500,000 IU may be associated with increased risks of falls and fracture.)[16]

Falls risk should be addressed at every opportunity. In Maureen and Kathleen, risks include visual impairment, cognitive impairment, use of antihypertensive medication and musculoskeletal disease. Although not all of these risks are remediable, consideration of a program such as 'Stepping On' (http://www.steppingon.com) may be appropriate.[17] A range of specific interventions have been assessed for falls prevention.[18] Strength and balance exercises are particularly important. Physiotherapy, occupational therapy or geriatric referrals, with consideration of a home visit, may be appropriate for tailored assessment of falls risk. A quick numerical assessment of falls risk can be made with tools such as the Falls Risk Assessment Tool (FRAT).[19]

Applying management principles to the case scenarios

Should bisphosphonate treatment be suspended in any of the three patients discussed?

The risks and benefits both of ceasing and of continuing therapy should be assessed. In an elderly woman with a previous fracture, the ongoing risk of fracture is high. In Maureen's case, the risk is compounded by her use of antihypertensive medications, the presence of eye disease contributing to falls risk, and her BMD in the osteoporotic range. With Maureen's low bone density, age, previous low trauma fracture and other medical problems, her risk of falls and fractures is high. The absence of further fracture, although reassuring, does not necessarily mean that she has had sufficient antiosteoporotic therapy. Although she has been taking therapy for eight years, the benefit of therapy is still likely to exceed the risk. Continuing some type of therapy would be prudent, with enquiry at each review regarding thigh pain and dental health.

In Kathleen's case, the decision is easier. The combination of further fracture and deteriorating bone density in a patient with multiple comorbidities, limited adherence to therapy, ongoing smoking, poor diet and low vitamin D level confers a high risk of future fracture. Some form of treatment should continue.

For Susan, with no further fracture and improved BMD, suspension of therapy is appropriate, with periodic review.

Should treatment be changed for Maureen or Kathleen?

Transfer to another agent such as an intravenous bisphosphonate or denosumab could be considered for tolerability or patient preference but is not always necessary. However, Kathleen can be considered to have treatment failure according to the criteria shown in Box 2. A change of therapy may be indicated.

Conclusion

Every patient taking antiosteoporotic therapy should be regularly reassessed regarding continuing therapy, with the ongoing risk of fracture balanced against the small risk of continued therapy. Consideration should be given to whether treatment remains appropriate, whether any change is warranted and whether any 'tweaking' is possible to lower risk, remembering nonpharmacological measures such as dietary improvement, falls prevention and smoking cessation. Each patient should be assessed for individual risk. Patients receiving ongoing antiresorptive therapy, particularly long term, should be asked regularly about thigh pain because of the small risk of AFF. MT

References

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

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Journal Watch on page 77.

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