New therapies for postmenopausal osteoporosis

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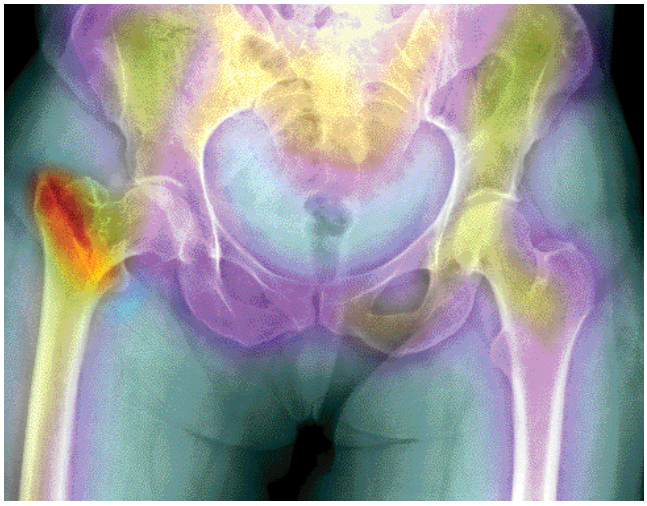

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Treatment selection for postmenopausal osteoporosis varies depending on the age of the woman and the presence or absence of menopausal symptoms.

The ideal treatment for postmenopausal osteoporosis should be both safe and efficacious in preventing vertebral and nonvertebral fractures, including hip fractures. Treatment selection may vary depending on the age of the woman and the presence or absence of menopausal symptoms. A critical part of any osteoporosis management strategy is maintaining adequate 25-hydroxyvitamin D levels and calcium intakes, either through diet or supplementation. This is particularly important in elderly women, many of whom may have limited exposure to sunlight and inadequate nutrition. Vitamin D deficiency should be corrected before patients are given intravenous bisphosphonates to avoid hypocalcaemia. Increasing weight-bearing exercise is also important.

Pharmacological therapies for postmenopausal osteoporosis are classified into two categories: anticatabolic and anabolic agents. However, strontium ranelate (Protos) does not clearly fit into either category as it decreases bone resorption and increases markers of bone formation.

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Anticatabolic agents

Anticatabolic drugs reverse the negative bone balance seen in patients with osteoporosis by decreasing high rates of bone remodelling. This is achieved by preferentially decreasing bone resorption. In the short term before bone formation also decreases, bone balance becomes positive but thereafter remains in equilibrium, explaining why increases in bone mineral density (BMD) are largest during the first year of therapy.

Most current therapies for osteoporosis are anticatabolic. Among the available anticatabolic therapies, oestrogen and the bisphosphonates alendronate (Alendro, Fosamax, Fosamax Plus [with cholecalciferol]) and risedronate (Actonel, Actonel Combi [with calcium carbonate]) reduce vertebral and nonvertebral fractures. The effect of the modified oestrogen tibolone (Livial) is to reduce osteoporotic fracture risk in older women, but it has been associated with a modest increase in stroke risk and is not recommended for long-term osteoporosis therapy.

Alendronate and risedronate have both demonstrated robust fracture risk reductions – approximately 40 to 50% reduction in vertebral fracture risk, 30 to 40% in nonvertebral fracture risk, and 40 to 50% in hip fracture risk.[1,2] Women taking part in these studies were predominantly elderly and postmenopausal.

The new anticatabolic drugs are:

- oral and intravenous ibandronic acid (Bonviva)
- the intravenous bisphosphonate zoledronic acid (Zometa, Aclasta)
- subcutaneous human monoclonal antibody against the receptor activator of nuclear factor-κB ligand (RANK-L), denosumab.

Table 1 provides information on the availability of these drugs.

Oral ibandronic acid

Ibandronic acid, a new bisphosphonate administered orally once a month, has demonstrated efficacy in reducing vertebral fracture risk. It reduces nonvertebral fractures in a subset of women with a low bone density (T-score <-3.0). It also increases bone density and prevents bone loss in women in the early postmenopausal stages.

In a randomised, double-blinded study, 2946 postmenopausal women received oral ibandronic acid administered either every day (2.5 mg) or intermittently (20 mg every other day for 12 doses every three

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Table 1. New therapies for osteoporosis: PBS information and availability*

Generic name	Registered name	PBS listing and availability
Ibandronic acid	Bonviva	Listed on PBS but not currently available in Australia
Zoledronic acid	Zometa	Available, but not PBS listed for osteoporosis
	Aclasta	Not available in Australia
Denosumab	N/A	Not available in Australia
Teriparatide (human PTH [1-34])	Forteo	Available, but not PBS listed
Strontium ranelate	Protos	PBS listed April 2007 (authority required, streamlined)†

* As of 1 October 2007. † PBS restrictions for strontium ranelate apply. For more information visit www.pbs.gov.au/html/healthpro/home (accessed September 2007).

months) or placebo. After three years, daily and intermittent oral ibandronic acid significantly reduced the risk of vertebral fractures by 62 and 50%, respectively, versus placebo. This was the first study to show that intermittently administered bisphosphonates significantly reduces fracture risk.[3]

The Monthly Oral Ibandronate in Ladies (MOBILE) study compared the efficacy of three once monthly oral regimens of ibandronic acid (2 x 50 mg given on two consecutive days, 100 mg, and 150 mg) with daily oral ibandronic acid (2.5 mg) in women with postmenopausal osteoporosis. This two-year study suggests that the 150 mg monthly regimen provides a greater therapeutic efficacy in postmenopausal osteoporosis than the daily or 100 mg monthly regimen.[4] The usual dose of oral ibandronic acid is 150 mg per month.

Side effects

Oral administration of ibandronic acid may be associated with upper gastrointestinal side effects, particularly in patients with gastro-oesophageal reflux disease. Its use may also rarely be associated with osteonecrosis of the jaw (discussed below).

Intravenous bisphosphonates

Ibandronic acid

In the Intermittent Regimen Intravenous Ibandronate Study (IRIS), 520 women in the late stages of the menopause and with a lumbar spine BMD T-score of less than -2.5, were randomised to receive either 2 mg or 1 mg ibandronic acid intravenous injections, given once every three months for one year, or placebo. Lumbar spine BMD increased by 5.0% in women who received 2 mg ibandronic acid compared with a decrease of 0.04% in the placebo group. Total hip BMD also increased by 2.9% in women in the 2 mg group.[5] Serum and urinary C-telopeptide of type 1 collagen (CTX), both markers of bone resorption, decreased by 62.5% and 61.0%, respectively, in the 2 mg group. No indicators of renal toxicity were reported. A larger study using intravenous ibandronic acid (DIVA Study) has recently been completed.

Ibandronic acid is given as a rapid intravenous injection over 15 to 30 seconds.

Zoledronic acid

Zoledronic acid has been evaluated in a large study of postmenopausal women in which the administration of an annual 4 mg dose resulted in equivalent increases in BMD and decreases in bone turnover than did lower doses administered more frequently.[6] A 5 mg dose (Aclasta) has been studied in osteoporosis, whereas the 4 mg dose (Zometa) is used in cancer treatment.

A pivotal study investigating the antifracture efficacy of zoledronic acid in postmenopausal women with osteoporosis (HORIZON) showed that an annual infusion of zoledronic acid (5 mg) over a three-year period significantly reduced the risk of vertebral fracture by 70%, nonvertebral fractures by 25% and hip fracture by 41% compared with placebo.[7] There was a small increase in the absolute risk of atrial fibrillation of 0.8% in the zoledronic acid group, but no other adverse events were identified. There was one case of osteonecrosis of the jaw in both treatment and placebo groups.

A recent study of 2127 elderly patients who had had a hip fracture showed that an annual infusion of zoledronic acid (5 mg) reduced the risk of clinical fractures by 35% and mortality by 28% compared with placebo.[8] Pyrexia, myalgia and musculoskeletal pain were the most common side effects, but no cases of osteonecrosis of the jaw were reported and fracture healing was unimpaired. Atrial fibrillation and stroke rates were similar in the two groups. In the elderly after hip fracture, the risk–benefit profile appears to favour treatment with zoledronic acid; however, additional long-term safety data will be important.

Zoledronic acid is given as an intravenous infusion over 15 minutes

Side effects and precautions

Intravenous administration of ibandronic acid and zoledronic acid may be associated with early influenza-like symptoms and both have the potential for causing hypocalcaemia, particularly in those with vitamin D deficiency. Rarely, ocular side effects of iritis may occur. It is, therefore, important to check renal function (eGFR),

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and serum calcium and 25 hydroxyvitamin D concentrations, and to correct vitamin D deficiency prior to administering intravenous bisphosphonates.

Zoledronic acid may cause an increase in serum creatinine concentrations in patients with renal impairment and it has a longer skeletal half-life than ibandronic acid.

Rarely, bisphosphonates, both oral and intravenous, may be associated with osteonecrosis of the jaw in which there is presence of exposed bone in the oral cavity for more than eight weeks. It is most commonly seen in patients with bone malignancy and taking potent, high-dose intravenous bisphosphonates. The incidence seems to be low, with estimates ranging from one in 10,000 to one in 100,000 patients who are taking oral bisphosphonates for osteoporosis.[9,10] The risk appears to be increased after dental extraction and in those with periodontal disease, therefore, good dental hygiene is important in patients taking bisphosphonates.

Denosumab

Denosumab is a human monoclonal antibody that binds to RANK-L, which is produced by stromal cells and osteoblasts. RANK-L stimulates osteoclast differentiation, activation and survival and also inhibits osteoclast apoptosis. Denosumab mimics the action of the endogenous inhibitor of RANK-L, osteoprotegerin, to inhibit activation of this ligand.

Denosumab, administered every six months as a subcutaneous injection at a dose of 60 mg, results in rapid decreases in bone resorption. The decreases in bone resorption are reversible. Increases in BMD after one year of treatment are similar to or greater than those seen with alendronate.[11] Large studies evaluating the efficacy of denosumab on fracture reduction in postmenopausal women are underway.

Side effects and precautions

Few side effects regarding the use of denosumab have been identified to date. One of the major precautions is to correct vitamin D deficiency and ensure adequate calcium nutrition in patients before denosumab is given.

Anabolic agents

There are two ways in which anabolic drugs act to induce a positive bone balance that persists long term:

- by activating the bone multicellular unit, resulting in a preferential increase in bone formation over bone resorption
- by increasing conversion of bone lining cells to osteoblasts, further increasing bone formation and resulting in a positive bone balance.

Parathyroid hormone

The most extensively studied form of parathyroid hormone (PTH) in osteoporosis is the PTH (1-34) fragment, teriparatide (Forteo). Teriparatide is the first available anabolic therapy. It significantly reduces the risk of vertebral and nonvertebral fractures. There are no data evaluating teriparatide on reducing risk of hip fracture. It is usually reserved for treatment of patients with severe osteoporosis or in whom anticatabolic therapy has failed.

Teriparatide is administered as a daily 20 µg subcutaneous injection in the thigh/abdomen area. Lifetime duration of treatment is 18 months or less. It is not listed on the PBS and is an expensive drug.

In the largest study of postmenopausal women with osteoporosis, PTH (1-34) 20 µg/day increased spinal and femoral neck BMD by 9% and 3%, respectively, over 22 months.[12] The risk of vertebral fractures and nonvertebral fractures were reduced by 65% and 53%, respectively. Bone histomorphometry studies showed increases in trabecular volume and cortical thickness by 38% and 25%, respectively. In addition, trabecular connectivity was increased. All these changes result in increased bone strength.

Teriparatide is also as effective at increasing BMD when administered in a cyclic fashion of three months on and three months off treatment. This may result from dissociation between the early phase of bone formation stimulation and the later activation of bone remodelling seen with continuous PTH therapy.

Side effects and precautions

Side effects of teriparatide include transient hypercalcaemia, nausea and headache. Oncogenicity studies in rodents showed an increased risk of osteogenic sarcoma, but this is not thought to be relevant in humans who have a lower relative duration of exposure.

Paget's disease, prior radiation therapy, metastatic bone disease, hypercalcaemia or unexplained increases in alkaline phosphatase are contraindications to the use of teriparatide. One case of osteogenic sarcoma has been seen in a patient taking this anabolic agent.

Important interactions

PTH treatment should not be coadministered with anticatabolic agents, as this will attenuate its effects on BMD and decrease effects on markers of bone formation. Sequential therapy is optimal with PTH therapy followed by anticatabolic therapy. Also, importantly, after PTH treatment, anticatabolic therapy results in further increases in BMD at both cortical and trabecular sites. The bone gained will be lost if no further anticatabolic therapy is initiated.

Treatment with bisphosphonates after PTH therapy not only conserves bone, but adds a further amount of bone equivalent to that from *de novo* bisphosphonate therapy. The anabolic effect of PTH is retained in patients previously treated with a bisphosphonate, although the effect may be smaller. The optimal interval between stopping a bisphosphonate and starting PTH therapy is uncertain.

Thus, combining anabolic and anticatabolic drugs diminishes the effects of the anabolic drug; sequential therapy is preferred.

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continued

Table 2. New therapies for osteoporosis: administration routes, dosages and effects

Drug	Administration and dosage	Effects
Ibandronic acid	Oral, 150 mg per month	Increases BMD
		Prevents bone loss in postmenopausal women in the early stages
		Reduces vertebral and nonvertebral fractures (in patients with T-score <-3.0)
		Does not reduce risk of hip fractures
	Intravenous, 2 mg per three months	Increases lumbar spine and total hip BMD
		Pending data on vertebral, nonvertebral and hip fractures
Zoledronic acid	Intravenous, 5 mg per year	Increases BMD
		Decreases bone turnover
		Reduces risk of vertebral, nonvertebral and hip fractures
		Reduces mortality in elderly after hip fracture
Denosumab	Subcutaneous, 60 mg per six months	Increases BMD
		Decreases bone resorption
		Pending fracture data
Teriparatide (human PTH [1-34])	Subcutaneous, 20 µg per day	Increases BMD
		Reduces risk of vertebral and nonvertebral fractures
		No hip fracture data
Strontium ranelate	Oral, 2 g per day	Increases BMD
		Reduces risk of vertebral, nonvertebral and hip fractures (in patients with T-score <-3.0)

Strontium ranelate

Strontium ranelate induces uncoupling in bone remodelling between formation and resorption of the bone. Although it stimulates bone formation and reduces bone resorption in normal bone in rats, mice and monkeys, human data on effects on bone formation have not yet been completed; therefore, it is uncertain whether it has an anticatabolic or anabolic action. Strontium ranelate may activate the calcium-sensing receptor to achieve its effects on bone remodelling.

The atomic number of strontium ranelate is greater than calcium so its presence in bone will weaken the penetration of x-rays and result in an overestimation of BMD. Formulae are used to correct spinal BMD, but not the BMD at other sites such as the hip. Strontium ranelate is given orally at a dose of 2 g per day.

A large phase III trial showed increased BMD and early and sustained reductions in the risk of vertebral fractures in postmenopausal women with osteoporosis taking oral strontium ranelate (2 g per day). There was no reduction in nonvertebral fractures.[13]

In the Treatment of Peripheral Osteoporosis Study (TROPOS), 5091 postmenopausal women with osteoporosis randomly received 2 g per day strontium ranelate or placebo. The results showed that the relative risk was reduced by 16% for all nonvertebral fractures and by 19% for all major fragility fractures including hip fractures at three years.[14]

Strontium ranelate is also effective in reducing fractures in those without pre-existing fractures and in patients older than 80 years of age. The combination of strontium ranelate and bisphosphonates is not recommended. There are no data showing the antifracture efficacy of strontium ranelate therapy following bisphosphonate treatment.

Side effects

The most common side effect of strontium ranelate is diarrhoea; others include headache, nausea and rash. Upper gastrointestinal side effects are uncommon. There is also a slight increase in the incidence of deep venous thrombosis with strontium ranelate.

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Conclusion

New drugs for the management of postmenopausal osteoporosis include strontium ranelate, which has been shown to reduce vertebral and nonvertebral fracture risk, and zoledronic acid, a potent injectable bisphosphonate that increases BMD with only once yearly intravenous administration. Zoledronic acid has also recently been shown to reduce risk of vertebral, nonvertebral and hip fractures. Zoledronic acid treatment after hip fracture in the elderly is also associated with a reduction in mortality. Denosumab reduces bone turnover and increases BMD with six-monthly subcutaneous administration. Tables 1 and 2 summarise the effects, administration routes and dosages and availabilities of these new osteoporosis therapies.

Many current treatments are effective in reducing fractures due to osteoporosis and more are in development.[15] The selection of safe therapies to reduce bone loss shortly after the menopause, however, remains problematic. New draft osteoporosis guidelines (prepared by the NHMRC and RACGP) will be available late in 2007 and should help GPs make an informed choice of the most appropriate treatment for their patients. MT

A list of references is available on request to the editorial office.

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DECLARATION OF INTEREST: Professor Ebeling has received research funding or acted as a consultant for Amgen, Novartis and Merck Sharp and Dohme.

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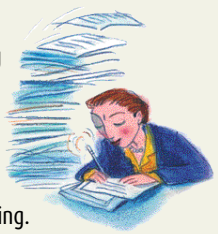

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