Where now for the management of osteoporosis?

Ignac Fogelman

Osteoporosis is a metabolic bone disorder, leading to bone fragility and fracture. Recent guidance from the National Institute for Clinical Excellence (NICE) emphasizes the importance of secondary prevention of fragility fractures in postmenopausal women. What impact can the expanding range of treatments make on the growing and costly burden of osteoporosis?

Osteoporosis is the most common metabolic bone disorder, leading to bone fragility and fracture. One in three women over the age of 50 will sustain a vertebral fracture, and one in six will have a hip fracture (National Institute for Clinical Excellence (NICE), 2005). Twenty per cent of people who have a vertebral fracture will have a second within 1 year (Lindsay et al, 2001), and forearm fractures increase the risk of subsequent hip fracture by about 50% (Cuddihy et al, 1999).

In view of the ageing population and the move away from routine use of hormone replacement therapy (HRT) to prevent osteoporosis because of safety concerns (Rossouw et al, 2002), fragility fractures are likely to present a growing challenge to both primary and secondary care physicians over coming decades. In the UK, for example, an estimated £1.5–1.8 billion was spent on the treatment of osteoporotic fractures in 2000, a figure that is predicted to rise to £2.1 billion by 2010 (NICE, 2005).

The risk factors for osteoporosis in women are well known. These include family history, early menopause, smoking, low body mass index (<19 kg/m^2), long-term use of high dose corticosteroids, and co-morbidities, such as thyrotoxicosis and hyperparathyroidism.

Diagnosis can be confirmed by bone mineral density measurement (BMD) using dual energy X-ray absorptiometry (DXA scans). The World Health Organization classification of osteoporosis uses the number of standard deviations (SDs) from the BMD in an average 25-year-old woman (T-score) (*Table 1*) (World Health Organization, 1994). Osteoporosis is classed as a T-score of below 2.5.

This article discusses the advantages and disadvantages of established and newer treatments for osteoporosis, and considers what issues should be addressed when tailoring treatment to individual needs.

THE IMPORTANCE OF CALCIUM AND VITAMIN D

Whatever treatment is chosen for osteoporosis, it is important to optimize levels of calcium and vitamin D. While daily calcium supplements of 1 g or more reduce bone loss in women with osteoporosis (Royal College of Physicians, 2000), calcium alone does not appear to affect fracture rate (Shea et al, 2003) and, in isolation, must be considered a weak treatment. In the UK, many people live in a relatively vitamin D deficient state for much of the year because of the absence of sunshine. It is important to correct this deficiency where it exists. Calcium supplementation, in combination with vitamin D, has been shown to reduce hip fractures by 26% over 3 years, and all non-vertebral fractures by 28% (Gillespie et al, 2003).

However, preliminary data from the randomized trial of vitamin D and calcium for the secondary prevention of osteoporosis-related

TABLE 1.
Bone mineral density (BMD) values in the diagnosis of osteoporosis

Diagnosis	T-score
Normal	T-score > -1 SD
Osteopenia	T-score -1 – -2.5 SD
Osteoporosis	T-score < -2.5 SD
Established osteoporosis	T-score < -2.5 SD + one or more osteoporotic fractures

SD = Standard deviation, T-score = Number of SDs from the BMD in an average 25-year-old woman. From World Health Organization, 1994.

Professor Ignac Fogelman is Professor of Nuclear Medicine, Guy's, King's and St Thomas' School of Medicine, Guy's Hospital, London SE1 9RT

fractures in the elderly (RECORD) did not support routine supplementation (Grant et al, 2005). This study of over 5000 men and women aged 70 years or more, who had already experienced a low trauma fracture failed to show any effect of daily calcium (1 g as carbonate), vitamin D3 (800iu/20µg), or combination treatment on fracture risk. Recruitment to the study commenced in 1999, with follow-up ending in 2004. The full results are expected to be published shortly.

BISPHOSPHONATES

The bisphosphonates (alendronate, etidronate and risedronate) are the mainstay of osteoporosis treatment, although upper-gastrointestinal (GI) side-effects limit their use is some patients. Bisphosphonates inhibit bone resorption and may lead to a modest increase in BMD by inhibiting osteoclastic activity.

Alendronate (Fosamax) 10 mg/day is licensed for the treatment of osteoporosis in postmenopausal women to prevent fractures (NICE, 2005). A once-weekly oral preparation (70 mg) is also licensed for the treatment of postmenopausal osteoporosis and is generally the preferred option.

Etidronate (Didronel) 400 mg/day is licensed for the treatment of osteoporosis (NICE, 2005), and is taken in 90-day cycles: etidronate for 14 days followed by calcium carbonate (1.25 g/day) for 76 days.

Risedronate (Actonel) 5 mg/day is licensed for the treatment of postmenopausal osteoporosis, to reduce the risk of vertebral fractures, and for the treatment of established postmenopausal osteoporosis, to reduce the risk of hip fractures (NICE, 2005). As with alendronate, it is available and usually taken as a once-weekly preparation (35 mg/week).

While the design and robustness of the fracture trials carried out on the three drugs varies, reductions in vertebral fractures in the order of 37–57% have been reported, as well as reductions of 34–51% for hip fractures, and reductions of 19–48% for wrist fractures (NICE, 2005).

The main adverse effects of bisphosphonate treatment are nausea, dyspepsia, mild oesophagitis and/or gastritis and abdominal pain. Patients are advised to take bisphosphonates (alendronate and risedronate) with a glass of water, on an empty stomach, at least 30 minutes before food and to remain upright for at least 30 minutes after administration. Patients taking etidronate should not eat for 2 hours before or after treatment.

Bisphosphonates should be used cautiously when given to patients with active GI problems (NICE, 2005).

SELECTIVE OESTROGEN RECEPTOR MODIFIERS (SERMS)

The only SERM currently licensed for the treatment of osteoporosis in postmenopausal women is raloxifene (Evista) 60 mg/day. As with bisphosphonates, raloxifene works by inhibiting bone resorption.

In the raloxifene study carried out in women with osteoporosis, raloxifene 60 mg was associated with a reduction in vertebral fractures of 30% at 3 years, but there was no significant effect on non-vertebral fractures (Ettinger et al, 1999).

Results did, however, suggest a protective effect against breast cancer, with an overall 4-year reduction in breast cancer of 72% (Cauley et al, 2001). Hopes that raloxifene could have a beneficial effect on cardiovascular disease have not yet been confirmed, but there is evidence that it lowers fibrinogen and total and low density lipoprotein-cholesterol (Nice, 2005).

Raloxifene is associated with a slight increased risk of venous thromboembolism, and women may also experience side effects, including hot flushes, arthralgia, dizziness and leg cramps (Nice, 2005).

Raloxifene should not be prescribed to women with a history of venous thromboembolism, hepatic impairment, cholestasis, severe renal impairment, undiagnosed uterine bleeding, and endometrial cancer. Nor should it be co-administered with systemic oestrogens or given to women undergoing breast cancer treatment.

PARATHYROID HORMONE

Teriparatide (Forsteo) is a recombinant form of human parathyroid hormone and is a potent anabolic agent which stimulates the formation of new bone, and is licensed for the treatment of established osteoporosis in postmenopausal women. The recommended dose is 20 µg/day by subcutaneous injection in the thigh or abdomen.

Teriparatide 20 µg/day has been shown to reduce vertebral fractures by 65% and non-vertebral fractures by 53%, over a median 21 months, in women with previous vertebral fractures (Neer et al, 2001).

This drug is well tolerated, but nausea and headache are the most common side effects. However, it cannot be prescribed to women with pre-existing hypercalcaemia, severe renal impairment, metabolic bone diseases other than primary osteoporosis (including hyperparathyroidism and Paget's disease of the bone), unexplained eleva-

tions of alkaline phosphatase, and previous radiation therapy to the skeleton. There are occasional reports of hypercalcaemia with its use.

STRONTIUM RANELATE

Strontium ranelate (Protelos) is the first dual action bone agent to be licensed for the treatment of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures. It increases bone formation by stimulating pre-osteoblast replication, and decreases bone resorption by inhibiting osteoclast activity and differentiation (Marie et al, 2001).

Strontium ranelate is a tasteless powder, with a recommended daily dose of one 2 g sachet in water each day, preferably taken at bedtime, at least 2 hours after eating, as bioavailability may be reduced by food, milk, dairy products and calcium salts.

In clinical trials of women with osteoporosis, strontium ranelate has been associated with a 41% reduction in new vertebral fractures over 3 years (Meunier et al, 2004), and with a 16% reduction in non-vertebral fractures (Reginster et al, 2005). The reduction in vertebral fractures was associated with an improvement in health related quality of life (HRQOL) (Meunier et al, 2004).

Among women at high risk of hip fracture (age >74 years and femoral neck BMD T-score <-3), strontium ranelate has been shown to reduce the relative risk for hip fracture by 36% (Reginster et al, 2005).

Strontium ranelate appears to be well tolerated, with low levels of upper gastro-intestinal problems. In clinical trials, the most common adverse events were nausea and diarrhoea, which were generally reported at the beginning of treatment with levels comparable with the placebo (Meunier et al, 2004).

TAILORING TREATMENT TO PATIENT NEEDS

In its UK guidance on bisphosphonates, selective oestrogen receptor modulators and parathyroid hormone for the secondary prevention of osteoporotic fragility fractures in postmenopausal women, NICE (2005) recommended bisphosphonate treatment as first-line therapy for the secondary prevention of osteoporotic fragility fractures in women aged 75 years and older. More restrictive criteria for treatment in younger women have been widely criticized, but this is not the forum to discuss this further.

For women who do not obtain a satisfactory response to bisphosphonates, are intolerant to them, or cannot comply with the special recommendations for administration, or for whom treatment is contraindicated, NICE recommends raloxifene.

Teriparatide is recommended for women aged over 65 years who have fractures while on conventional treatment, who have very low bone density, or are continuing to lose bone.

Strontium ranelate was not available when the current guidance was drawn up, but will be considered in a separate NICE appraisal, scheduled for publication at the beginning of 2006.

Physicians will already have recognized the need for choice in the management of osteoporosis, as some patients will not be able to tolerate a bisphosphonate. There is research (Yood et al, 2003) and anecdotal evidence that at least a third of patients stop taking bisphosphonates within 1 year of starting treatment. Side-effects and perceived lack of efficacy are the most likely reasons. Ease of administration is also important, and the requirement to take bisphosphonates on an empty stomach, and to stand or sit upright for 30 minutes after administration may deter some women from adhering to treatment. Raloxifene is generally well tolerated, although 'menopausal' type symptoms are a problem in some cases, and other patients are concerned about the slight increased risk of thrombosis. Clinical experience will show whether the bedtime dosing schedule for strontium ranelate can encourage better compliance rates.

CONCLUSIONS

A large and growing population of women is at risk of osteoporosis; however, fewer than 1 in 5 of those with the condition may be receiving drug treatment (NICE, 2005). There is good evidence that effective treatment can reduce osteoporotic fractures and this should, in turn, reduce the disability and mortality associated with osteoporosis.

No single treatment will suit all women and efficacy, tolerability and ability to comply with administration requirements should all be considered when assessing the appropriateness of treatment. HM

Conflict of interest: none

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KEY POINTS

- Osteoporosis is the most common metabolic bone disorder, and prevalence increases with age.
- One in three women over the age of 50 years will sustain a vertebral fracture, and 1 in 6 will have a hip fracture.
- Calcium and vitamin D levels should be optimized in all women with osteoporosis.
- The main treatments for osteoporosis are bisphosphonates (alendronate, etidronate and risedronate), raloxifene, teriparatide and strontium ranelate.
- In women with osteoporosis, these treatments can reduce vertebral fractures by at least 40% and hip fractures by about 30%.
- Choice of treatment is likely to depend on efficacy, tolerability and ease of administration.