

Quality use of medicines: the postmenopausal woman with osteoporosis

Andy Gray, Julia Botha and Deon Hoffman

Department of Experimental and Clinical Pharmacology
Nelson R Mandela School of Medicine
University of Natal

Correspondence: Email: graya1@nu.ac.za

Guidelines for the management of any condition suffer the ravages of time and can be challenged even by the publication of a single study. This may well apply to any guidelines that include hormone replacement therapy (HRT), such as the Osteoporosis Clinical Guideline published in 2000 by the South African Medical Association.¹ Noting that "reliable comparative data on the various drugs registered for the treatment of osteoporosis are not available", the Osteoporosis Working Group attempted to guide clinicians' drug choices. They suggested that, in women with menopausal symptoms or at risk of coronary heart disease, HRT should be considered, if not contraindicated or contrary to the patient's preferences. That comfortable world was overturned in May 2002. One arm of the Women's Health Initiative (WHI) trial - a controlled trial involving 16 608 postmenopausal women, randomised to receive continuous conjugated oestrogen plus progestogen or placebo - was stopped when it became evident that the overall risks exceeded the benefits.² It has been reported that, within a month, 30% of long-term HRT users in the United States stopped taking their hormones. However, it was estimated that one in five took no alternative steps to protect their bones.³ How might a family practitioner react if confronted by such a scenario or by a newly diagnosed postmenopausal woman with osteoporosis? Can a P-drug analysis provide some answers?

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The first step is to define the problem clearly, as do the SAMA guidelines: "osteoporosis is a systemic skeletal disease characterised by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture". Bone mineral density (BMD) is the most quantifiable predictor of fracture risk for those who have not yet suffered a fragility fracture. Values should of course be viewed in the context of the age of the patient. A diagnosis of osteoporosis can be made when the T-score is below -2.5 (i.e. the patient's BMD is at least 2.5 standard deviations below the mean for a young adult female). Severe osteoporosis describes patients who have, in addition, suffered a fragility fracture. The therapeutic objective is to reduce the frequency of vertebral and non-vertebral fractures (especially at the hip).⁴ Interventions are therefore sought that can ensure the

retention of bone mass and preserve the structural integrity of the skeleton, thus preventing fragility fractures. Critically, it must be recognised that changes in BMD are surrogate markers of effectiveness, whereas the real test of any intervention is its ability to prevent fractures in vertebral and non-vertebral bones.

Analysis of the relative efficacy, safety, suitability and cost should consider the following main groups: calcium (and vitamin D), hormone replacement therapy (HRT), selective oestrogen receptor modulators (SERMS) and the bisphosphonates. As the literature on these agents is extensive, it is useful to look for good quality systematic reviews and meta-analyses that can provide some data in the absence of direct comparative trials.

CALCIUM

Calcium is obviously an important

nutrient in the prevention and treatment of osteoporosis and, if not adequately provided in the diet, should be supplemented. Guidelines have consistently recommended that calcium (and vitamin D) should not be used or relied upon as sole treatments of osteoporosis.^{1,5,6} There is limited evidence for an independent effect on fracture occurrence. A 1997 systematic review of four randomised trials of calcium supplements (mean calcium dose: 1050mg) showed relative risks (RR) between 0.3 and 0.7 in those randomised to receive the supplements.⁷ Observational studies had inconsistent findings with RRs between 0.3 and 2.0. Nevertheless, calcium is considered an essential adjunct to other treatments and in most clinical trials of other agents both the active and placebo groups receive 500-1000mg calcium daily. A variety of calcium salts, in chewable and effervescent forms, are available for

between about R40 and R160 per month. However, it is important to watch the elemental calcium content, which can vary from 27-1000mg per dosage form. Vitamin D products are not reviewed in any depth here but should not be discounted completely, especially in frail, institutionalised patients. The more difficult choice is between the previously suggested first choice, HRT, and the newer and more expensive SERMS and bisphosphonates.

HRT AND SERMS

The increased rate of bone resorption after menopause clearly indicates an hormonal influence on bone mass. There are numerous randomised controlled trials (RCTs) showing a positive effect of HRT on BMD of both the spine and the hip. The North American Position Statement cited 50 such studies, with increases in spine BMD of the order of 4-6% and hip BMD of 2-3%.⁶ In 2001, Torgerson and Bell-Syer conducted a meta-analysis of 22 RCTs of the effect of HRT on non-vertebral fractures. They showed an overall significant reduction in such fracture and claimed that the effects were greater in those aged less than 60 years (RR 0.67, 95% CI 0.46-0.98, $p=0.03$) compared to those over 60 years (RR 0.88; 95% CI 0.71-1.08, $p=0.22$).⁸ This sub-group analysis was criticised in a subsequent letter and also an accompanying editorial.^{9,10} The latter pointed out that 21 of the 22 RCTs reviewed were not intended primarily to investigate the effects of HRT on fractures, and that consequently they did not enrol women with known osteoporosis. Also, the data for those aged more than 60 years came from just two studies, one of which was HERS II. The HERS II study showed a non-significant overall increase in fracture risk (relative hazard 1.04; 95% CI 0.87-1.25), but less than 20% of the women enrolled had osteoporosis as demonstrated by bone density.¹¹

The JAMA editorial was thus of the opinion that HERS II results "provide no data concerning the effectiveness of estrogen in older women with osteoporosis". In contrast, when the continuous, combined oestrogen-

progestin arm of the WHI study was terminated after 5.2 years, it did show a significantly decreased risk of fracture at all sites (RR 0.76; 95% CI 0.69 - 0.85), including the hip.² The balance between this efficacy and the potential risks was clearly stated: in exchange for 5 fewer hip fractures (per 10 000 person-years of treatment) and 6 fewer colorectal cancers, there would be 7 more coronary heart disease events, 8 more strokes, 8 more pulmonary emboli and 8 more invasive breast cancers. Given the overall conclusion "overall health risks exceeded benefits", could HRT still be considered a first-line option in a postmenopausal woman who was no longer requiring relief of vasomotor symptoms, and who might require many years of treatment for established osteoporosis? The ease of administration and the low cost (in the R130-R170 per month range) would seem not to compensate for the demonstrated lack of long-term safety.

The SERMS (such as raloxifene) have oestrogen agonist effects on bone and lipid metabolism and oestrogen antagonist action on the breast and uterus. In the MORE study, involving 7705 late postmenopausal women with osteoporosis, raloxifene reduced the risk of vertebral fractures by 30-50%, the reduction being statistically significant for women both with, and without, vertebral fracture at baseline. The risk of non-vertebral fracture was not significantly reduced (RR 0.9; 95% CI 0.8-1.1).¹² Patients experience an increase in hot flashes and venous thrombo-embolism, though reported infrequently (RR 3.1; 95%CI 1.5-6.2), was a serious side effect. In addition, 3-4 years of raloxifene administration was shown to decrease the risk of invasive breast cancer in postmenopausal women by 76%. However it has been pointed out that these patients were elderly and selected on the basis of osteoporosis criteria and therefore were not at increased risk of breast cancer.⁶ While easy to take, the SERMs are expensive, at about R500 per month.

BISPHOSPHONATES

It has in the past been easier to dismiss the bisphosphonates, based either on cost (about R450 per month) or

suitability. Both alendronate and risedronate can cause gastrointestinal upsets, varying from mild to moderate GI discomfort (dyspepsia, abdominal pain, diarrhoea) to rare instances of oesophagitis. Patients must take these drugs with a glass of water at least half an hour before a meal, and remain upright for an hour afterwards.¹³ Compliance with this should be easier with the new once weekly dosing forms of alendronate, sold at the same price as the daily version. This group of drugs inhibits osteoclast activity and thus reduces bone resorption. The Canadian guidelines, which rated the level of evidence for each consensus statement, concluded that "alendronate and risedronate are efficacious in preventing vertebral and non-vertebral fractures", rating this as Level 1 evidence.⁵ These guidelines therefore considered bisphosphonates as first line choices for the treatment of postmenopausal women with osteoporosis, especially in those with pre-existing vertebral fractures. It must be remembered though that the oral bioavailability of bisphosphonates is low, (between 1 and 3%), and that absorption is impaired by food, calcium, iron, coffee, tea and orange juice. It is therefore important to stick to the dosing instructions. The half-life of bisphosphonates in bone is several years, and many more years of experience will be necessary before any definite answers about the safety of long-term use are obtained. The optimum duration of treatment is also unknown - findings of one study suggest that 7 years of treatment with alendronate is safe, but there may not be additional benefit after 5 years based on changes of BMD and bone turnover markers.¹⁴ Recently some serious ocular side effects, including vision-threatening scleritis, have been reported for bisphosphonates.¹⁵ Since this information comes from several spontaneous reporting systems, there are no data on incidence but it does seem to be very rare. While such reports are more frequent with pamidronate than alendronate, etidronate and risedronate (221, 180, 21 and 10 reports respectively) this may merely reflect the usage to date of each medication. In a subsequent letter, the authors warned physicians look out for "deep boring eye pain, a red eye, photophobia and decreased

vision" and refer to an ophthalmologist.¹⁶ Scleritis is vision-threatening and potentially blinding if unrecognized and untreated, and none of the cases of unilateral or bilateral scleritis resolved, regardless of therapy, until the bisphosphonate was discontinued.

OTHER AGENTS

A number of other agents have been investigated. Pharmacological doses of calcitonin inhibit osteoclast activity but, being a polypeptide, it cannot be given by mouth. There is a higher incidence of side effects with the injectable formulation than with the nasal spray, although anaphylaxis and other severe allergic reactions are possible with both. Parathyroid hormone (teriparatide) has recently been registered by the FDA. Fluoride is not recommended for the treatment of postmenopausal women with osteoporosis. No evidence exists to recommend additional intakes of magnesium, copper, zinc, phosphorus, manganese, iron or essential fatty acids. A number of other agents are also reviewed in the South African guidelines.¹

CONCLUSION

A proposed summary of the evidence is offered in Table 1.

In conclusion, the family physician, faced with a postmenopausal woman with osteoporosis who is scared by the

media storm surrounding HRT, has a difficult choice to make. While the efficacy of the bisphosphonates seems to exceed that of the SERMs, both groups are expensive and carry small risks of dire side effects. Once weekly dosing of alendronate is attractive, perhaps outweighing the inconvenience of the normal dosing regimen. Starting a newly diagnosed case on HRT is difficult to justify, unless vasomotor symptoms demand short-term management. As the SAMA guidelines suggested, the choice of pharmacological agent will depend on the nature and staging of the disease, the patient's characteristics, the approach of the treating physician and the available resources. Delmas and Fraser have pointed to the high human cost of not treating osteoporosis – that is clearly not an option.¹⁷ □

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Please refer to the CPD questionnaire on page 61.

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Table 1: Multi-attribute utility analysis

Drug	Efficacy		Safety	Suitability	Cost
	Vertebral fractures	Non-vertebral fractures			
HRT	+	+	-	**	**
SERM (raloxifene)	++	0	*	**	-
Bisphosphonate (alendronate)	+++	++	*	*	-

Key:
 • for efficacy: +++ = strong evidence; ++ = good evidence; + = some evidence; 0 = no effects
 • for safety, suitability and cost: ** = very desirable features; * = desirable features; - = undesirable features