

Comparative effects of antiresorptive agents on bone mineral density and bone turnover in postmenopausal women

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Abstract: Postmenopausal osteoporosis is a common clinical entity; its complications represent a significant burden to society. In recent years the choice of therapies available for the treatment of postmenopausal osteoporosis has increased dramatically. There are a number of antiresorptive agents currently available including hormone replacement therapy (HRT), selective estrogen receptor modulators (SERMs), bisphosphonates, and dual action bone agents. It is difficult to truly compare these therapies given the lack of direct head-to-head studies. The efficacy of antiresorptive therapies can be assessed in a number of ways including measurement of bone mineral density (BMD), assessment of bone turnover markers, and fracture reduction. Other important factors include ease of administration and consequent patient compliance. This article reviews the currently available antiresorptive agents and their effects on the above outcome measures.

Keywords: osteoporosis, postmenopausal, fracture, antiresorptive agents

Background

Postmenopausal osteoporosis is a common clinical entity; its complications represent a significant burden to society. The lifetime risk of any fracture occurring in women from the age of 50 years is currently greater than 40% and it is anticipated that the prevalence of osteoporosis will rise in the coming decades as the longevity of the population increases. In addition to the negative impact on a patient's level of independence and quality of life, the economic cost of osteoporotic fractures also needs to be taken into account. In the UK the estimated acute hospital cost of an osteoporotic hip fracture is approximately £12 000 sterling, with non-acute hospital costs representing an even larger amount. Other fractures are less expensive, at £468, £479, and £1338 respectively for wrist, vertebral, and other fractures. The annual cost of treating all female osteoporotic fractures in the UK is £727 million. Assuming each male hip fracture costs the same as a female fracture, including these would increase the total costs to 942 million pounds (Dolan and Torgerson 1998). It has been predicted that the cost of treating osteoporotic fractures in postmenopausal women will increase to more than 2.1 billion pounds by 2020 (Burge 2001).

Osteoporotic fractures can have a detrimental impact on an individual's level of independence, quality of life, and potential mortality. Hip fractures lead to a greater risk of functional impairment and institutionalization. Chronic pain and disability among patients with vertebral fractures are significantly greater on average than among people without fractures, even after adjusting for co-morbid conditions that are common among the elderly. The risk of pain and disability increases progressively with the number and severity of vertebral deformities. Declines in physical function

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and changes in appearance with loss of height contribute to social isolation and loss of self-esteem (Ross 1997).

In osteoporotic patients mortality is increased in the first year after all major fractures, with age-standardized mortality ratios of 2.18 for proximal femoral fractures and 1.66 for vertebral fractures (Center et al 1999).

In recent years the choice of therapies available for the treatment of postmenopausal osteoporosis has increased dramatically. There are a number of antiresorptive agents currently available including hormone replacement therapy, selective estrogen receptor modulators, bisphosphonates, and dual action bone agents (Table 1).

Bone mineral density

Measurement of bone mineral density (BMD) by dual energy X-ray absorptiometry (DEXA) remains the gold standard for the diagnosis of osteoporosis and is frequently used as a primary end-point in osteoporosis treatment trials. A patient's BMD is expressed by its relationship in standard deviations from two norms, the expected BMD of a young adult of the same sex (T score) and the expected BMD of an age and sex matched individual (Z score). There are limitations of BMD measurements in the assessment of osteoporosis. Analyses of clinical trials show an inconsistent relationship between increased spinal BMD and a decreased risk of vertebral fracture. Increased BMD accounts for less than 25% of the overall reduction in fracture risk in most instances. Although helpful in guiding decisions to initiate osteoporosis treatment, subsequent changes in BMD provide an imperfect indicator of treatment efficacy. Consequently, fracture risk reduction itself remains the most clinically relevant therapeutic outcome of osteoporosis therapy (Small 2005).

Bone turnover

Increasing evidence suggests that a high rate of bone turnover is associated with low BMD and is strongly linked to fracture risk. Measurement of biochemical markers of bone turnover is therefore becoming a more widely used end-point in clinical trials in postmenopausal osteoporosis. Biochemical markers of bone resorption and formation can be measured in the blood and urine. Frequently used markers of resorption include deoxypyridinoline, which is measured in urine, and amino- and carboxy-terminal cross-linked telopeptides of type 1 collagen (NTx, CTx), which may be measured in serum or urine. Bone formation markers include osteocalcin, bone-specific alkaline phosphatase and amino-terminal propeptide of type 1 collagen.

Early changes in biochemical markers of bone turnover predict BMD response to antiresorptive therapy and may potentially identify non-responders to therapy. Significant decreases in both type 1 collagen N-telopeptide and osteocalcin are evident in women treated with antiresorptive agents as early as 3 months while the percent change of N-telopeptide at 3 months has been shown to correlate with change of spinal BMD at 12 months of treatment (Kim et al 2005).

Hormone replacement therapy

The role of estrogen deficiency in postmenopausal osteoporosis is well established and for many years hormone replacement therapy (HRT) was used as first-line therapy. The sudden reduction in estrogen production with the menopause is responsible for an accelerated phase of bone loss. Estrogen deficiency at the onset of menopause is associated with increased production of pro-resorptive cytokines. The rate of bone remodelling doubles at menopause, triples 13 years after menopause, and remains high if osteoporosis occurs (Recker et al 2004). The use of long-term HRT has been limited by evidence of association with increased risk of breast cancer (Beral 2003). It is now advised that HRT is used for the shortest time possible to prevent menopausal symptoms, but long-term administration for the prevention of osteoporosis is no longer advisable.

HRT and BMD

A number of studies have shown increased BMD at the lumbar spine and neck of femur in patients with established

Table 1 Effects of antiresorptive agents on BMD and fracture reduction in postmenopausal women with osteoporosis

	Lumbar spine BMD	Hip BMD	Risk of vertebral fracture	Risk of non-vertebral fracture
HRT	↑	↑	↓	↓
Raloxifene	↑	↑	↓	↔
Etidronate	↑	↑	↓	↔
Alendronate	↑	↑	↓	↓
Risedronate	↑	↑	↓	↓
Ibandronate	↑	↑	↓	Not yet ascertained
Strontium Ranelate	↑	↑	↓	↓
	Allow for bone strontium content	Allow for bone strontium content		

Abbreviations: BMD, bone mineral density; HRT, hormone replacement therapy.

osteoporosis following treatment with HRT in either oral or transdermal forms. Continuous low dose estrogen and progesterone therapy over a 3.5 year period increased spinal BMD by 3.5% ($p < 0.001$) in an intention-to-treat analysis and by 5.2% among patients with greater than 90% adherence to therapy (Recker et al 1999). Transdermal estrogen, when compared with placebo in a one-year study, showed a 5.3% versus 0.2% ($p = 0.007$) change in BMD at the lumbar spine and 7.6% versus 2.1% ($p = 0.03$) at the femoral trochanter (Lufkin et al 1992).

HRT and bone turnover

At the menopause markers of bone resorption and formation increase, but can be restored to premenopausal values with estrogen replacement. Combined estrogen/progestagen therapy compared with placebo over a 1 year period shows significantly decreased biochemical estimates of bone resorption (fasting urinary calcium and hydroxyproline) and bone formation (serum alkaline phosphatase and plasma osteocalcin) ($p < 0.001$). The reduction in indices of bone resorption was more pronounced than that in bone formation after one year, indicating a positive bone balance (Christiansen and Riis 1990).

Transdermal estrogen uniformly decreases bone turnover as assessed by serum osteocalcin concentration and histomorphometric evaluation of iliac biopsies. Biopsy samples confirmed the effect of estrogen on bone formation rate per bone volume (median change, -12.9% compared with -6.2% per year; $p = 0.004$) (Lufkin et al 1992).

In a separate study of the effectiveness of transdermal estrogen on BMD, patients were divided by measurement of whole body retention (WBR) of ^{99m}Tc -methylene diphosphonate into those with high and low bone turnover. The response to estrogen was greater in high bone turnover patients than in low bone turnover patients. BMD in the lumbar spine increased by 5.7% and 6.6% in high bone turnover patients and by 2.6% and 2.7% in low bone turnover patients after 1 and 2 years, respectively. Hence, the evaluation of bone turnover may be useful to identify those postmenopausal osteoporotic women who may especially benefit from treatment with estrogen (Gonnelli et al 1997).

HRT and clinical outcomes

As a result of uncertainties in the balance of risks and benefits for hormone replacement therapy, the Women's Health Initiative (WHI) was undertaken. This randomized controlled study of postmenopausal women observed rates

of coronary artery disease, breast cancer, stroke, pulmonary embolism, endometrial cancer and fractures. Participants were randomly assigned to receive estrogen plus medroxyprogesterone acetate or placebo. Fractures were experienced by 8.6% in the estrogen-progestin group and 11.1% in the placebo group (hazard ratio [HR] 0.76). The decreased risk of fracture attributed to estrogen plus progestin appeared to be present in all subgroups of women examined. After a mean of 5.2 years the estimated HRs were as follows: coronary artery disease 1.29, breast cancer 1.26, stroke 1.41, pulmonary embolism 2.13, and endometrial cancer 0.83. On this basis, the project management group concluded that the overall health risks exceeded the benefits from use of combined estrogen and progestin for an average 5.2 year follow-up in healthy postmenopausal women (Cauley et al 2003).

The reduction in fracture risk by estrogen exceeds that expected based on BMD alone. Estrogen therapy must be continued indefinitely for preservation of its anti-fracture efficacy. A decade after discontinuation of HRT, women will have a similar fracture risk to those who have not received therapy. Given the strong body of evidence supporting the effectiveness of HRT in preventing osteoporotic fractures, the challenge facing physicians is whether the benefits of HRT outweigh its risks.

Selective estrogen receptor modulators

The selective estrogen receptor modulators (SERMs) exert estrogenic activity in some target tissues, for example bone, while sparing the breast and endometrium from the undesirable stimulation caused by estrogen and as such are an alternative to hormone replacement therapies for the treatment of postmenopausal osteoporosis. Raloxifene is the only SERM licensed for the treatment of osteoporosis. Drawbacks of this therapy are menopausal symptoms of hot flashes, breast pain and vaginal bleeding and also increased incidence of thromboembolic events (Cosman et al 2005; Layton et al 2005; Romero et al 2005).

Raloxifene and BMD

A number of studies have shown the beneficial effect of raloxifene on BMD in postmenopausal osteoporosis (Delmas et al 1997; Lufkin et al 1998; Meunier et al 1999). The MORE trial (Multiple Outcomes of Raloxifene) was a multicenter, randomized, placebo-controlled study of 7705 postmenopausal women. Compared with placebo, raloxifene increased BMD in the femoral neck by 2.1% (60 mg) and

2.4% (120 mg) and in the spine by 2.6% (60 mg) and 2.7% (120 mg) ($p < 0.001$ for all comparisons) (Ettinger et al 1999).

Raloxifene and bone turnover

Raloxifene preserves bone mass by reducing elevated levels of bone turnover by mechanisms similar to those in postmenopausal women receiving hormone replacement therapy. In a randomized, controlled study of raloxifene and HRT, transiliac bone biopsies were obtained following double tetracycline labelling at baseline and 1 year. These samples were analyzed for changes in histologic indices of bone remodeling on the cancellous surface as well as at the endocortical subdivision of the endosteal envelope, the location of the greatest fraction of postmenopausal bone loss. BMD and biochemical markers of bone turnover were also determined at baseline and 1 year. Four paired biopsies were obtained in the HRT group, six in the raloxifene group, and five in the placebo group. The frequency of remodelling events on cancellous bone and rate of bone formation in both cancellous and endocortical bone increased in the placebo group, while these measurements decreased in both drug treatment groups. Serum bone alkaline phosphatase, serum osteocalcin, and urine C-terminal cross-linking telopeptide of type I collagen significantly decreased ($p < 0.05$) in both active treatment groups, changes significantly different than those seen with placebo (Weinstein et al 2003).

Raloxifene and fracture reduction

The MORE trial (Multiple Outcomes of Raloxifene) at 36 months showed a new vertebral fracture in 10.1% of women receiving placebo, 6.6% of those receiving 60 mg of raloxifene and 5.4% of those receiving 120 mg of raloxifene. Risk of vertebral fracture was reduced in both study groups treated with raloxifene (relative risk [RR] 0.7 for 60 mg, RR 0.5 for 120 mg). However the risk of nonvertebral fracture for raloxifene versus placebo did not differ significantly (Ettinger et al 1999).

In an extension of the MORE study a significant effect on nonvertebral fractures was seen only in patients with severe vertebral fractures at baseline (Delmas et al 2003).

Bisphosphonates

The bisphosphonate group of drugs are considered first line therapy for the treatment of postmenopausal osteoporosis. Bisphosphonates are stable chemical analogues of an inorganic pyrophosphate. They inhibit osteoclastic bone resorption via a mechanism that differs from that of other

antiresorptive agents. Bisphosphonates attach to bony surfaces particularly in sites of active resorption, reduce recruitment and activity of osteoclasts and increase their apoptosis (Rodan and Fleisch 1996).

Despite their structural similarities, there are important differences among the bisphosphonates in potency and toxicity. The mechanism by which the bisphosphonates increase the apoptosis of osteoclasts differs. The first generation of bisphosphonates included etidronate and tiludronate. The more potent second generation of bisphosphonates include alendronate, risedronate, and ibandronate. These nitrogen-containing bisphosphonates interfere with the mevalonate pathway and protein prenylation, while other bisphosphonates are incorporated into nonmetabolized analogs of adenosine triphosphate (ATP) (Reska and Rodan 2003, 2004; Rogers 2003).

Etidronate

Etidronate was the first bisphosphonate used in the treatment of postmenopausal osteoporosis. A seven year study determined the efficacy and safety of cyclical oral etidronate in the treatment of postmenopausal osteoporosis and examined the effects of discontinuing treatment after 2 or 5 years of therapy. The incidence and rate of vertebral fractures were lowest in patients with the longest exposure to etidronate. Bone mass was maintained for at least 2 years after treatment with etidronate was discontinued, however, further gains in spinal bone mass were seen in patients who continued therapy (Miller et al 1997).

Etidronate is available in both oral and intravenous preparations. However the administration of etidronate by prolonged intravenous infusion was inconvenient, and potentially associated with thrombotic complications and infections. Etidronate has been largely superseded by the other bisphosphonates.

Alendronate and BMD

Several studies have demonstrated the long-term efficacy of alendronate in the treatment of postmenopausal osteoporosis. (Harris et al 1993; Liberman et al 1993; Chestnut et al 1995; Black et al 1996; Tucci et al 1996; Hosking et al 1998).

Alendronate significantly increases BMD at the lumbar spine, hip and total body and is well tolerated in the treatment of osteoporosis in postmenopausal women. In a randomized, double-blind, placebo-controlled, 2-year study, 188 postmenopausal women showed mean changes in BMD over 24 months with 10 mg alendronate of +7.21% \pm 0.49%

for the lumbar spine, +5.27% \pm 0.70% for total hip, and +2.53% \pm 0.68% for total body ($p < 0.01$) compared with changes of -1.35% \pm 0.61%, -1.20% \pm 0.64% and -0.31% \pm 0.44% at these sites, respectively, with placebo treatment. (Chestnut et al 1995).

In a separate multinational study of postmenopausal women with lumbar spine t scores of ≤ -2 , subjects were randomly assigned to receive oral alendronate 10 mg ($n=950$) or placebo ($n=958$) once daily. At 12 months, mean increases in BMD were significantly greater in the alendronate than the placebo group by 4.9% at the lumbar spine, 2.4% at the femoral neck, 3.6% at the trochanter and 3.0% for total hip ($p \leq 0.001$) (Pols et al 1999).

Alendronate is the only bisphosphonate with ten year data. Treatment with 10 mg of alendronate daily for 10 years produced mean increases in BMD of 13.7% at the lumbar spine, 10.3% at the trochanter and 5.4% at the femoral neck. Discontinuation of alendronate resulted in a gradual loss of effect, as measured by BMD and biochemical markers of bone remodelling (Bone et al 2004).

Alendronate and bone turnover

To establish whether biochemical markers could be used to monitor alendronate treatment and predict long-term response in BMD, a randomized trial was undertaken in postmenopausal women treated with 5 mg of alendronate. Urine N-telopeptide cross-links of type I collagen and osteocalcin were measured at baseline and 6 months. Spinal, hip, and total body BMD was recorded at baseline and 24 months. Reductions in biochemical marker levels at 6 months correlated with change from baseline in BMD at 24 months (coefficient of correlation from baseline $[r] = -0.28$ to -0.31 for N-telopeptide, $r = -0.16$ to -0.25 for osteocalcin) (Ravn et al 1999).

Alendronate administered at 10 mg daily produces a reduction in mean urinary deoxypyridinoline/creatinine reduction of 47% at 3 months, and in mean serum osteocalcin of 53% at 6 months (Chestnut et al 1995).

Alendronate and fracture reduction

A phase III trial comparing alendronate and placebo over 3 years in postmenopausal women with low femoral BMD and at least one previous vertebral fracture at baseline showed a reduction in both vertebral and nonvertebral fractures. A lower incidence of one or more new vertebral fractures was detected by X-ray (8% vs 15% in the placebo group, RR 0.5). There were fewer clinically evident vertebral

fractures in the alendronate group (2.3% vs 5.0%, RR 0.4). There was an overall lower rate of any fracture, including hip and wrist fractures (14% vs 18%, RR 0.7). (Tucci et al 1996). The reduction in fracture incidence attributed to alendronate is similar in postmenopausal women older and younger than age 75 years (Ensrud et al 1997).

In postmenopausal women with low BMD, but no history of osteoporotic fracture, alendronate increased BMD and reduced the number of clinical fractures by 14%, compared with placebo. In women with low BMD but without vertebral fractures, 4 years of alendronate safely increased BMD and decreased the risk of first vertebral deformity (Cummings et al 1998).

To determine the effect of alendronate on the incidence of nonvertebral fractures, a meta-analysis was performed of all completed prospective, randomized, placebo-controlled alendronate trials of at least 2 years' duration (5 studies). In the placebo group ($n=590$), 60 women reported nonvertebral fractures during 1347 patient-years at risk (overall rate, 4.45 women with fractures per 100 patient-years at risk). In the alendronate group ($n=1012$), 73 women reported nonvertebral fractures during 2240 patient-years-at risk (overall rate, 3.26 women with fractures per 100 patient-years at risk). The estimated cumulative incidence of nonvertebral fractures after 3 years was 12.6% in the placebo group and 9.0% in the alendronate group (Karpf et al 1997).

Risedronate and BMD

In a study of 939 postmenopausal women with T scores of -2 or less and at least one vertebral fracture, treated with 5 mg of risedronate or placebo for three years, BMD at the lumbar spine, femoral neck, and trochanter increased by 5.4%, 1.6%, and 3.3%, respectively in the risedronate group, as compared with 1.1%, -1.2%, and -0.7%, respectively in the placebo group (Harris et al 2000). In a pooled analysis of all randomized trials with risedronate in women with low BMD but with no previous vertebral fracture, the mean lumbosacral spine and femoral neck density increased by 5.3% and 2.5%, respectively (Heaney et al 2002).

Risedronate and bone turnover

Changes in the level of biochemical markers of bone resorption with risedronate treatment for osteoporosis have been examined as a potential surrogate for the decrease in fracture risk. A group of 693 postmenopausal women with at least one vertebral deformity were assigned to receive either 5 mg of risedronate or placebo and followed over a

three year period. Reductions in urinary C-telopeptide (median 60%) and N-telopeptide (median 51%) at 3–6 months with risedronate therapy were significantly associated with the reduction in vertebral fracture risk (75% over 1 year and 50% over 3 years, $p < 0.05$). The relationships between vertebral fracture risk and changes from baseline in C-telopeptide and N-telopeptide were not linear. Little further improvement was seen in fracture benefit below a decrease of 55%–60% for C-telopeptide and 35%–40% for N-telopeptide, leading the authors to surmise that there may be a level of bone resorption below which there is no further fracture benefit (Eastell et al 2003).

In a study to determine bone safety and preservation of normal bone formation after 5 years of risedronate treatment histomorphometric assessment of paired transiliac bone biopsies was undertaken. No statistically significant differences in structural or resorption parameters of bone were seen between risedronate and placebo treatment groups. Double tetracycline labels indicating continuous bone turnover were identified in all biopsy specimens (Ste-Marie et al 2004).

Risedronate and fracture reduction

The VERT (Vertebral Efficacy with Risedronate Therapy) study group has shown the efficacy of risedronate in reducing both vertebral and nonvertebral fractures in postmenopausal women with a previous vertebral fracture. The three year rates of new vertebral fractures were 11% and 16% in the risedronate and placebo groups ($p = 0.003$). The rates of nonvertebral fractures were 5% and 8% respectively ($p = 0.02$) (Harris et al 2000). The risk of new vertebral fracture after 5 years of risedronate therapy is reduced by 59% ($p = 0.01$) (Sorensen et al 2003).

Risedronate reduces the risk of first vertebral fracture in postmenopausal osteoporotic women. In a placebo controlled trial of risedronate in patients without vertebral fracture at baseline and who had low lumbar spine BMD, the incidence of first vertebral fracture was 9.4% in those treated with placebo and 2.6% in those treated with risedronate at 3 years. The number of patients who would need to be treated to prevent one new vertebral fracture was 15 (Heaney et al 2002).

A placebo controlled trial demonstrated the efficacy of risedronate in preventing hip fracture in 5445 elderly women with osteoporosis. After three years of treatment, the incidence of hip fracture in patients aged 70–79 years, was 1.9% in the risedronate group compared with 3.2% in those

assigned to placebo ($p = 0.009$). However, a subset of patients aged 80 or older with at least one non-skeletal risk factor for hip fracture (poor gait or propensity to fall) was also examined and no significant difference was found in fracture rate between risedronate and placebo (McClung et al 2001).

Alendronate versus risedronate

The FACT study (Fosamax Actonel Comparison Trial) was a 1-year-head-to-head trial comparing the efficacy and tolerability of once weekly alendronate 70 mg and risedronate 35 mg for the treatment of postmenopausal osteoporosis. The percentage of patients who had measured BMD gains $\geq 3\%$ and $\geq 5\%$ after 12 months at the hip trochanter, total hip, femoral neck, and lumbar spine was analyzed. The percentage of patients who experienced any bone loss, and those with measured losses of 3% or more at these sites after 12 months, was also determined. A greater percentage of alendronate- than risedronate-treated patients had measured BMD gains ($\geq 0\%$) ($p < 0.05$) at all sites at 12 months. Significantly more ($p < 0.01$) alendronate- than risedronate-treated patients had measured gains in BMD $\geq 3\%$ and $\geq 5\%$ at the hip trochanter, total hip, and lumbar spine. Significantly more ($p < 0.05$) risedronate- than alendronate-treated patients had an apparent loss of BMD ($> 0\%$ and $\geq 3\%$ loss) at the same sites.

The percentage of patients achieving reductions in urinary N-telopeptide of type 1 human collagen (NTX) $\geq 40\%$, and serum C-telopeptide of type 1 collagen (CTx) $\geq 60\%$, bone-specific phosphatase (BSAP) $\geq 30\%$, and N terminal propeptide of type 1 procollagen (PINP) $\geq 50\%$ at 3 months and 12 months was also determined. After 3 months, significantly more alendronate- than risedronate-treated patients achieved predefined reductions in all biochemical markers ($p < 0.001$).

The clinical significance of these BMD and bone turnover findings is unclear as no fracture data was accumulated in the study (Sebba et al 2004). The FACT study was sponsored by Merck Sharp Dome, the makers of alendronate. In patients aged 70–79 years, risedronate reduces the risk of hip fracture by 60% (McClung et al 2001). Alendronate reduces hip fracture by 51% in patients aged 55–81 years (Black et al 1996). These studies are not directly comparable given the different age groups of the patients involved. A meta-analysis of bisphosphonate therapy in preventing hip fractures shows a number needed to treat of 29 for risedronate and 91 for alendronate therapy (Deal 2002). When compared with calcitonin, risedronate has a

68% RR reduction in nonvertebral fractures at 6 months, while alendronate has a 28% RR reduction (Watts et al 2004).

Ibandronate introduction

Adherence to therapy is a concern in postmenopausal osteoporosis. Reducing oral bisphosphonate-dosing frequency is one measure available to improve this. It has previously been shown that postmenopausal women prescribed a weekly bisphosphonate had significantly better compliance than those taking daily bisphosphonates (Cramer et al 2005). However, compliance and persistence rates for both daily and weekly regimens are suboptimal, suggesting that less frequent dosing intervals may provide an opportunity to further improve the consistent use of bisphosphonate therapy.

Ibandronate is a potent, nitrogen-containing bisphosphonate. It can be administered either orally or as an intravenous injection, with a between-dose interval of greater than two months. In addition to increased convenience, the availability of once-monthly ibandronate may improve tolerability by reducing the potential for upper gastrointestinal irritation that can result from frequent, repeated exposure.

Ibandronate and BMD

The BONE (oral iBANDRONATE Osteoporosis vertebral fracture trial in North America and Europe) trial determined that ibandronate with dose-free intervals of greater than 2 months provided similar anti-fracture efficacy to daily dosing. Daily and intermittent ibandronate significantly increased BMD in the spine in both North American (5.4% and 4.4% vs baseline with daily and intermittent ibandronate, respectively) and European (7.1% and 6.3% vs baseline, respectively) populations. Significant increases were also observed for total hip BMD (2.6% and 3.7% vs baseline for daily, and 2.5% and 3.1% for intermittent; North American and European populations, respectively) (Chestnut et al 2005).

The monthly oral ibandronate therapy in postmenopausal osteoporosis (MOBILE) study compared once-monthly and daily ibandronate. A total of 1609 women were assigned to one of four oral ibandronate regimens: 2.5 mg daily, 50/50 mg monthly (single doses, consecutive days), 100 mg monthly or 150 mg monthly. After 1 year, lumbar spine BMD increased by 3.9%, 4.3%, 4.1%, and 4.9% in the 2.5 mg, 50/50 mg, 100 mg, and 150 mg arms, respectively. All monthly regimens were proven non-inferior, and the 150 mg

regimen superior, to the daily regimen. All monthly regimens produced similar hip BMD gains, which were larger than those with the daily regimen (Miller et al 2005).

Two year results from the MOBILE study showed substantial increases in lumbar spine BMD (5.0%, 5.3%, 5.6% and 6.6%) in the daily and once-monthly groups (50 mg + 50 mg, 100 mg and 150 mg), respectively. Substantial increases in proximal femur BMD (total hip, femoral neck, trochanter) were observed in all groups; 150 mg produced the most pronounced effect ($p < 0.05$ vs daily) (Reginster et al 2006).

Ibandronate and bone turnover

The BONE study demonstrated that ibandronate, administered both daily and intermittently, produced comparable, significant decreases in biochemical markers of bone turnover. A reduction in urinary excretion of C-telopeptide levels of 53.5% and 67.1% versus baseline for daily, and 50.0% and 53.8% for intermittent (North American and European populations, respectively) was observed ($p < 0.004$ for all cited measurements in each ibandronate group versus placebo) (Chestnut et al 2005). The MOBILE trial showed similar decreased levels of C-telopeptide in all regimens (daily and once-monthly groups 50 + 50 mg, 100 mg and 150 mg) (Cramer et al 2005). The 150mg regimen consistently produced greater C-telopeptide suppression than the 100 mg and daily regimens (Miller et al 2005).

Ibandronate and fracture reduction

In the BONE study consistent, significant efficacy in fracture prevention was observed in the North American (new vertebral fracture risk reduction: 60% and 54% with daily and intermittent ibandronate, respectively) and European patient populations (50% and 48%, respectively). Both ibandronate regimens also significantly reduced the incidence of new, worsening, and acute clinical, vertebral fractures (Chestnut et al 2005).

Zoledronate

Zoledronate is currently the most potent bisphosphonate licensed for the treatment of malignant hypercalcemia, but is not yet licensed for the treatment of osteoporosis. A placebo controlled trial of zoledronate, administered at 3 or 6 monthly intervals to postmenopausal women with osteoporosis increased BMD in all dosing regimens and

induced a sustained reduction in bone resorption markers (Reid et al 2002). A phase III study of zoledronate with fracture as end-point is currently ongoing.

Dual action bone agents – strontium ranelate

Strontium ranelate has a unique dual mechanism of action in that it simultaneously increases bone formation and decreases bone resorption. It is an orally active agent consisting of two atoms of stable strontium and an organic moiety, namely ranelic acid. In vitro studies show that strontium ranelate increases bone formation by increasing osteoblast precursor replication and collagen synthesis, and reduces bone resorption by decreasing osteoclast differentiation and resorption activity (Baron and Tsouderos 2002; Takahashi et al 2003). The presence of strontium in bone influences BMD measurement by DEXA scanning. An adjustment factor (10% overestimation for 1mol/mol% strontium) can be used to calculate the true BMD (Nielsen et al 1999).

Strontium ranelate and BMD

Two randomized studies have investigated the effect of strontium ranelate on BMD in postmenopausal women with osteoporosis, using BMD at the lumbar spine as a primary efficacy endpoint and femoral BMD as a secondary outcome measure.

The STRATOS study (Strontium ranelate: dose-dependent effects in established postmenopausal vertebral osteoporosis) enrolled 353 osteoporotic women with at least one previous vertebral fracture and a lumbar T-score ≤ -2.4 . Patients were randomized to receive placebo, 0.5 g, 1 g, or 2 g of strontium daily for 2 years. Lumbar BMD, adjusted for bone strontium content, increased in a dose-dependent manner from 1.4% with 0.5 g/day strontium to 3.0% with 2 g/day strontium, which was significantly higher than placebo ($p < 0.01$) (Meunier et al 2002).

The prevention of early postmenopausal bone loss by strontium ranelate (PREVOS) trial showed at two years, strontium ranelate (1 g/day) significantly increased lumbar BMD compared with placebo (+5.53%; $p < 0.001$) for measured values and also for values adjusted for bone strontium content (+1.41%; $p < 0.05$). Femoral neck and total hip BMD were also significantly increased compared with placebo, but values adjusted for strontium content were not given (Reginster et al 2002).

Strontium ranelate and bone turnover

Clinical trials have mainly focused on fracture reduction outcomes, however in both the SOTI (Spinal Osteoporosis Therapeutic Intervention) and TROPOS (Treatment of Peripheral Osteoporosis) studies, bone alkaline phosphatase increased and C-telopeptide decreased in all patients treated with strontium ranelate compared with placebo at all time points (Meunier et al 2004; Reginster et al 2005).

Strontium ranelate and fracture reduction

The anti-fracture effect of strontium ranelate has been demonstrated in two placebo-controlled phase III studies.

The SOTI trial demonstrated a reduced relative risk of new vertebral fracture over three years in postmenopausal females with established osteoporosis and a previous vertebral fracture. New vertebral fractures occurred in fewer patients in the strontium ranelate group than the placebo group, with a risk reduction of 49% in the first year of treatment and 41% during the three-year study period (RR, 0.59) (Meunier et al 2004).

The TROPOS study examined the effect of long-term treatment with strontium ranelate on vertebral and nonvertebral fractures in 5000 postmenopausal women with osteoporosis. Nonvertebral fracture was the predetermined main evaluation criterion. Over three years, treatment with strontium ranelate was associated with a 16% reduction in nonvertebral fractures (hip, wrist, pelvis, sacrum, ribs) relative to placebo. In a subgroup of women who were designated as being at high risk of nonvertebral fractures on account of their age and femoral BMD, the relative risk of hip fracture was reduced by 36% following treatment with strontium ranelate. The risk of sustaining a new vertebral fracture was reduced by 45% over 1 year and 39% over 3 years (Reginster et al 2005).

In patients over 80 years of age at inclusion, a pooled analysis of SOTI and TROPOS studies showed a reduction in RR of sustaining a new vertebral fracture of 32% over 3 years of strontium ranelate treatment (incidence of 19.1% with strontium ranelate and 26.5% with placebo).

Conclusion

Nonpharmacologic measures should be recommended to all postmenopausal women, including adequate exercise, a calcium rich diet, smoking cessation and avoidance of excessive alcohol intake. Calcium and vitamin D

supplementation are vital in those found to be deficient. Most osteoporotic fractures other than vertebral fractures are associated with falls. Factors such as muscle weakness, impaired vision, poor balance, and the use of medications that can cause drowsiness need to be taken into account in postmenopausal women at risk of osteoporotic fractures. A greater emphasis needs to be placed on fall prevention and patient education.

When used in association with such nonpharmacologic measures, antiresorptive therapy is effective in reducing fracture risk and the significant associated morbidity and mortality of postmenopausal osteoporosis. For many years the mainstay of treatment for postmenopausal osteoporosis had been HRT. However given concerns regarding risk benefit ratio, HRT is no longer used as first line therapy. SERMs used as a single agent have proven efficacy in fracture reduction and increasing BMD and may yet play an additional role as combination therapy with other antiresorptive agents.

The first generation bisphosphonates have been largely superseded by second generation agents such as risedronate and alendronate that have superior fracture reduction efficacy, particularly at the hip. The advent of once weekly bisphosphonate therapy was a major advance in improving patient compliance. The debate continues with regard to the superiority of continuous or intermittent treatment with bisphosphonates. The development of bisphosphonate therapies with longer dosage free intervals is an area of ongoing interest. Antifracture efficacy and safety of these intermittent bisphosphonate regimens needs to be demonstrated. Regardless of which bisphosphonate is used, there is a paucity of long-term data suggesting the optimal duration of treatment with bisphosphonate therapy.

The dual action bone agent strontium ranelate is an alternative for the treatment of postmenopausal osteoporosis. As antifracture efficacy in the lumbar spine has been demonstrated with this agent, it should be considered for those most at risk of vertebral fracture. Another potential indication for the use of strontium ranelate is in those who are intolerant of bisphosphonate therapy

Anabolic agents are now being employed in the treatment of postmenopausal osteoporosis. Recombinant human parathyroid hormone (PTH) stimulates bone formation, in contrast to antiresorptive agents. Recent investigations involving PTH, alone and in combination or sequential regimens with antiresorptive agents, have provided a greater understanding of the place of PTH in the armamentarium against osteoporosis. These studies indicate that adding a

bisphosphonate to PTH in previously untreated individuals does not produce additional bone benefit (Black et al 2003). However, sequential use of PTH followed by alendronate is highly effective at increasing BMD (Black et al 2005).

Potential novel antiresorptive agents are undergoing research. Recent new insights in our understanding of osteoclast differentiation have focused our attention on osteoprotegerin and receptor activator of NF- κ B (RANK) ligand. A fully human monoclonal antibody to RANK ligand has been developed which has proven antiresorptive effects in reducing urinary N-telopeptide (Bekker et al 2004). Cathepsin K, a protease secreted by osteoclasts, is another potential therapeutic target for the treatment of postmenopausal osteoporosis. Estrogen deficient primates injected subcutaneously with cathepsin K inhibitor were shown to have a 42% reduction in C-terminal telopeptide and a 34% reduction in N-telopeptide (Stroup et al 2001).

From this overview we can clearly see that there are a large number of effective treatments currently available for postmenopausal osteoporosis. Despite this it is difficult to truly compare these therapies given the lack of direct head-to-head studies. A number of questions remain unanswered. The possibility of combining anti-resorptive therapies has not as of yet been fully explored. This therapeutic option may further improve clinical outcomes and fracture reduction.

References

- Baron R, Tsouderos Y. 2002. In vitro effects of S12911-2 on osteoclast function and bone marrow macrophage differentiation. *Eur J Pharmacol*, 450:11-17.
- Bekker PJ, Holloway DL, Rasmussen AS, et al. 2004. A single-dose placebo-controlled study of AMG 162, a fully human monoclonal antibody to RANKL, in postmenopausal women. *J Bone Miner Res*, 20:2275-82.
- Beral V; Million Women Study Collaborators. 2003. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet*, 362:1160.
- Black DM, Bilezikian JP, Ensrud KE, et al. 2005. One year of alendronate after one year of parathyroid hormone (1-84) for osteoporosis. *N Engl J Med*, 353:555-65.
- Black DM, Cummings SR, Karpf DB, et al. 1996. Randomized trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. *Lancet*, 348:1535-41.
- Black DM, Greenspan SL, Ensrud KE, et al. 2003. The effects of parathyroid hormone and alendronate alone or in combination in postmenopausal osteoporosis. *N Engl J Med*, 349:1207-15.
- Bone HG, Hosking D, Devogelaer JP, et al. 2004. Ten years' experience with alendronate for osteoporosis in postmenopausal women. *N Engl J Med*, 350:1189-99.
- Burge RT. 2001. The cost of osteoporotic fractures in the UK. Projections for 2000-2020. *J Med Econ*, 4:51-62.

- Cauley JA, Robbins J, Chen Z, et al. 2003. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. *JAMA*, 290:1729-38.
- Center JR, Nguyen TV, Schneider D, et al. 1999. Mortality after all major types of osteoporotic fracture in men and women: an observational study. *Lancet*, 353:878-82.
- Chestnut CH 3rd, McClung MR, Ensrud KE, et al. 1995. Alendronate treatment of the postmenopausal osteoporotic woman: effect of multiple dosages on bone mass and bone remodeling. *Am J Med*, 99:144-52.
- Chestnut CH, Ettinger MP, Miller PD, et al. 2005. Ibandronate produces significant, similar efficacy in North American and European women: new clinical findings from BONE. *Curr Med Res Opin*, 21:391-401.
- Christiansen C, Riis BJ. 1990. 17 Beta-estradiol and continuous norethisterone: a unique treatment for established osteoporosis in elderly women. *J Clin Endocrinol Metab*, 71:836-41.
- Cosman F, Baz-Hecht M, Cushman M, et al. 2005. Short-term effects of estrogen, tamoxifen and raloxifene on hemostasis: a randomized-controlled study and review of the literature. *Thromb Res*, 116:1-13.
- Cramer JA, Amonkar MM, Hebborn A, et al. 2005. Compliance and persistence with bisphosphonate dosing regimens among women with postmenopausal osteoporosis. *Curr Med Res Opin*, 21:1453-60.
- Cummings SR, Black DM, Thompson DE, et al. 1998. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. *JAMA*, 280:2119-20.
- Deal CL. 2002. Risedronate prevents hip fractures, but who should get therapy? *Cleve Clin J Med*, 69:964-76.
- Delmas PD, Bjarnason NH, Mitlak BH, et al. 1997. Effects of raloxifene on bone mineral density, serum cholesterol concentrations, and uterine endometrium in postmenopausal women. *N Engl J Med*, 337:1641-7.
- Delmas PD, Genant HK, Crans GG, et al. 2003. Severity of prevalent vertebral fractures and the risk of subsequent vertebral and nonvertebral fractures: results from the MORE trial. *Bone*, 33:522-32.
- Dolan P, Torgerson DJ. 1998. The cost of treating osteoporotic fractures in the United Kingdom female population. *Osteoporos Int*, 8:611-17.
- Eastell R, Barton I, Hannon RA, et al. 2003. Relationship of early changes in bone resorption to the reduction in fracture risk with risedronate. *J Bone Miner Res*, 18:1051-6.
- Ensrud KE, Black DM, Palermo L, et al. 1997. Treatment with alendronate prevents fractures in women at highest risk: results from the Fracture Intervention Trail. *Arch Intern Med*, 157:2617-24.
- Ettinger B, Black DM, Mitlak BH, et al. 1999. Reduction of vertebral fracture risk in postmenopausal women treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. *JAMA*, 282:637-45.
- Gonnelli S, Cepollaro C, Pondrelli C, et al. 1997. The usefulness of bone turnover in predicting the response to transdermal estrogen therapy in postmenopausal osteoporosis. *J Bone Miner Res*, 12:624-31.
- Harris ST, Gertz BJ, Genant HK, et al. 1993. The effect of short term treatment with alendronate on vertebral density and biochemical markers of bone remodelling in early postmenopausal women. *J Clin Endocrinol Metab*, 76:1399.
- Harris ST, Watts NB, Genant HK, et al. 2000. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. *JAMA*, 283:1424-5.
- Heaney RP, Zizic TM, Fogelman I, et al. 2002. Risedronate reduces the risk of first vertebral fracture in osteoporotic women. *Osteoporos Int*, 13:501-5.
- Hosking D, Chilvers CE, Christiansen C, et al. 1998. Prevention of bone loss with alendronate in postmenopausal women under 60 years of age. Early Postmenopausal Intervention Cohort Study Group. *N Engl J Med*, 338:485-92.
- Kanis JA, Johnell O, Oden A, et al. 2000. Long-term risk of osteoporotic fracture in Malmo. *Osteoporos Int*, 11:669-74.
- Karpf DB, Shapiro DR, Seeman E, et al. 1997. Prevention of nonvertebral fractures by alendronate. A meta-analysis. Alendronate Osteoporosis Treatment Study Groups. *JAMA*, 277:1159-64.
- Kim SW, Park do J, Park KS, et al. 2005. Early changes in biochemical markers of bone turnover predict bone mineral density response to antiresorptive therapy in Korean postmenopausal women with osteoporosis. *Endocr J*, 52:667-74.
- Layton D, Clarke A, Wilton LV, et al. 2005. Safety profile of raloxifene as used in general practice in England: results of a prescription-event monitoring study. *Osteoporos Int*, 16:490-500.
- Liberman UA, Weiss SR, Broll J, et al. 1995. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group. *N Engl J Med*, 333:1437.
- Lufkin EG, Wahner HW, O'Fallon WM, et al. 1992. Treatment of postmenopausal osteoporosis with transdermal estrogen. *Ann Intern Med*, 117:1-9.
- Lufkin EG, Whitaker MD, Nickelsen T, et al. 1998. Treatment of established postmenopausal osteoporosis with raloxifene: a randomized trial. *J Bone Miner Res*, 13:1747-54.
- McClung MR, Geusens P, Miller PD, et al. 2001. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. *N Engl J Med*, 344:333-40.
- Meunier PJ, Roux C, Seeman E, et al. 2004. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. *N Engl J Med*, 350:459-68.
- Meunier PJ, Slosman DO, Delmas PD, et al. 2002. Strontium ranelate: dose-dependent effects in established postmenopausal vertebral osteoporosis - a 2-year randomized placebo controlled trial. *J Clin Endocrinol Metab*, 87:2060-6.
- Meunier PJ, Vignot E, Garnero P, et al. 1999. Treatment of postmenopausal women with osteoporosis or low bone density with raloxifene. Raloxifene Study Group. *Osteoporos Int*, 10:330-6.
- Miller PD, McClung MR, Macovei L, et al. 2005. Monthly oral ibandronate therapy in postmenopausal osteoporosis: 1-year results from the MOBILE study. *J Bone Miner Res*, 20:1315-22.
- Miller PD, Watts NB, Licata AA, et al. 1997. Cyclical etidronate in the treatment of postmenopausal osteoporosis: efficacy and safety after seven years of treatment. *Am J Med*, 103:468-76.
- Nielsen SP, Slosman D, Sorensen OH, et al. 1999. Influence of strontium on bone mineral density and bone mineral content measurements by dual X-ray absorptiometry. *J Clin Densitom*, 2:371-9.
- Pols HA, Felsenberg D, Hanley DA, et al. 1999. Multinational, placebo-controlled trial of the effects of alendronate on bone density and fracture risk in postmenopausal women with low bone mass: results of the FOSIT study. Fosamax International Trial Study Group. *Osteoporos Int*, 9:461-8.
- Ravn P, Hosking D, Thompson D, et al. 1999. Monitoring of alendronate treatment and prediction of effect on bone mass by biochemical markers in the early postmenopausal intervention cohort study. *J Clin Endocrinol Metab*, 84:2363-8.
- Recker R, Lappe J, Davies KM, et al. 2004. Bone remodelling increases substantially in the years after menopause and remains increased in older osteoporosis patients. *J Bone Miner Res*, 19:1628-33.
- Recker RR, Davies KM, Dowd RM, et al. 1999. The effect of low-dose continuous estrogen and progesterone therapy with calcium and vitamin D on bone in elderly women. A randomized, controlled trial. *Ann Intern Med*, 130:897-904.
- Reginster J, Seeman E, Vernejoul M, et al. 2005. Strontium ranelate reduces the risk of non-vertebral fractures in postmenopausal women with osteoporosis: TROPOS study. *J Clin Endocrinol Metab*, 90:2816-22.
- Reginster JY, Adami S, Lakatoa P, et al. 2006. Efficacy and tolerability of once-monthly oral ibandronate in postmenopausal osteoporosis: 2-year results from the MOBILE study. *Ann Rheum Dis*, 65:654-61.

- Reginster JY, Deroisy R, Dougados M, et al. 2002. Prevention of early postmenopausal bone loss by strontium ranelate: the randomized, two-year, double-masked, dose-ranging, placebo controlled PREVOS trial. *Osteoporos Int*, 13:925-31.
- Reid IR, Brown JP, Burckhardt P, et al. 2002. Intravenous zoledronic acid in postmenopausal women with low bone mineral density. *N Engl J Med*, 346:653-61.
- Reska AA, Rodan GA. 2004. Nitrogen-containing bisphosphonate mechanism of action. *Mini Rev Med Chem*, 4:711-19.
- Reska AA, Rodan GA. 2003. Mechanism of action of bisphosphonates. *Curr Osteoporos*, 1:45-52.
- Rodan GA, Fleisch HA. 1996. Bisphosphonates: mechanisms of action. *J Clin Invest*, 97:2692-6.
- Rogers MJ. 2003. New insights into the molecular mechanisms of action of bisphosphonates. *Curr Pharm Des*, 9:2643-58.
- Romero A, Alonso C, Rincon M, et al. 2005. Risk of venous thromboembolic in women. A qualitative systematic review. *Eur J Obstet Gynecol Reprod Biol*, 121:8-17.
- Ross PD. 1997. Clinical consequences of vertebral fractures. *Am J Med*, 103:30S-42S.
- Sebba AI, Bonnick SL, Kagan R, et al. 2004. Response to therapy with once-weekly alendronate 70 mg compared to once-weekly risedronate 35mg in the treatment of postmenopausal osteoporosis. *Curr Med Res Opin*, 20:2031-41.
- Small RE. 2005. Uses and limitations of bone mineral density measurements in the management of osteoporosis. *MedGenMed*, 9:3.
- Sorensen OH, Crawford GM, Mulder H, et al. 2003. Long-term efficacy of risedronate: a 5-year placebo-controlled clinical experience. *Bone*, 32:120-6.
- Ste-Marie LG, Sod E, Johnson T, et al. 2004. Five years of treatment with risedronate and its effects on bone safety in women with postmenopausal osteoporosis. *Calcif Tissue Int*, 75:469-76.
- Stroup GB, Lark MW, Veber DF, et al. 2001. Potent and selective inhibition of human cathepsin K leads to inhibition of bone resorption in vivo in a nonhuman primate. *J Bone Miner Res*, 16:1739-46.
- Takahashi N, Sasaki T, Tsouderos Y, et al. 2003. S12911-2 inhibits osteoclastic bone resorption in vitro. *J Bone Miner Res*, 18:1082-7.
- Tucci JR, Tonino RP, Emkey RD, et al. 1996. Effect of three years of oral alendronate treatment in postmenopausal women with osteoporosis. *Am J Med*, 101:488.
- Watts NB, Worley K, Solis A et al. 2004. Comparison of risedronate to alendronate and calcitonin for early reduction of nonvertebral fracture risk: results from a managed care administrative claims database. *J Manag Care Pharm*, 10:142-51.
- Weinstein RS, Parfitt AM, Marcus R, et al. 2003. Effects of raloxifene, hormone replacement therapy, and placebo on bone turnover in postmenopausal women. *Osteoporos Int*, 14:814-22.

