Fracture protection in osteoporosis with risedronate

Steven Boonen, Dirk Vanderschueren

Osteoporosis is a major public health problem in the UK, and will become even more common as the population ages. This article will review osteoporosis management and a first-line treatment, risedronate (Actonel), which has been shown to preserve bone quality and reduce the risk of both vertebral and non-vertebral fractures within 6 months of initiation of therapy.

Osteoporosis is a major public health problem throughout the world (Cummings and Melton, 2002). The UK is no exception, with one in three women and one in 12 men aged over 50 years sustaining an osteoporosis-related fracture in their lifetime (National Osteoporosis Society, 2003). Currently, about 3 million people in the UK have osteoporosis (National Osteoporosis Society, 2003), and in 2000 the cost of treating the resulting 190 000 fractures was estimated at £1.8 billion (Bose et al, 2001). Since osteoporosis is an age-related condition, this already large economic burden will increase substantially as the population ages, and it has been suggested that by 2020 the total number of osteoporosis-related fractures each year will increase by over 21% to 230 000, with costs rising by 20% to over £2.1 billion (Bose et al, 2001).

Osteoporosis is also costly for affected individuals. An osteoporosis-related fracture is associated with increased difficulty in activities of daily living (ADL), fear, anxiety and depression (National Institutes of Health (NIH) Consensus Development Panel, 2001). One year after hip fracture, one third of men and one fifth of women will have died (Cooper, 1997; Autier et al, 2000; Haentjens et al, 2001). In those who survive, two fifths are unable to walk independently, nearly two thirds require help with one essential ADL (e.g. dressing, bathing, preparing food), and over three quarters are unable to perform at least one instrumental ADL (e.g. driving, shopping, cleaning) (Boonen et al, 2004a).

Increased mortality is also seen in people with vertebral fractures, although the fractures may not in themselves cause death but may indicate the presence of comorbid conditions that increase the risk (Cooper, 1997). Only about one third of vertebral fractures are diagnosed clinically (Cooper, 1997), but these too cause back pain, reduced quality of life and functional limitation (Nevitt et al, 1998).

CHANGING DEFINITIONS OF OSTEOPOROSIS

Defined by the Royal College of Physicians/Bone and Tooth Society (RCP/BATS) (2000) as a progressive, systemic, skeletal disease characterized by low bone mass and microarchitectural deterioration of bone, osteoporosis occurs after longitudinal growth has ceased when bone resorption by the osteoclasts begins to outpace the ability of the osteoblasts to form new bone (Seeman, 2002).

In the UK, identification of an individual with osteoporosis is based on either their bone mineral density (BMD), their fracture status or both. The World Health Organization and the International Osteoporosis Federation have developed four dual energy X-ray absorptiometry (DXA)-based diagnostic categories for women, in which BMD values are given as T-scores – that is standard deviations (SD) from BMD in the young healthy population. Whether similar cut-off values apply to men remains to be clarified (Kanis, 2002).

At present, most clinicians diagnose and treat osteoporosis based on BMD measurements. Because low BMD is a strong risk factor for future fracture, densitometry is an excellent diagnostic tool to identify postmenopausal women who are most at risk and who would benefit from antiresorptive treatment. However, as a monitoring tool once the patient is on treatment, densitometry has significant limitations. Research has demonstrated that BMD increases as a result of antiresorptive therapy are actually only a small contributing factor to bone strength and therefore fracture risk reduction (Boonen et al, 2004b).

Professor Steven Boonen is Professor of Medicine and **Professor Dirk Vanderschueren** is Professor of Medicine, Leuven University Center for Metabolic Bone Diseases, Katholieke Universiteit Leuven, Leuven, Belgium

Correspondence to: Professor S Boonen

Even for potent bisphosphonates like alendronate and risedronate, less than 30% of the fracture risk reduction can be explained by increases in BMD.

So while measurement of bone quantity can be useful in predicting future fracture risk and in identifying those individuals who are likely to benefit most from antiresorptive treatment, measuring increases in BMD over time will not necessarily give an accurate reading of how effective the treatment is at reducing the incidence of fractures (Cummings and Melton, 2002; Watts et al, 2002). This is significant in light of the fact that fracture prevention, rather than building BMD, has become the main treatment goal for osteoporosis (NIH Consensus Development Panel, 2001). From a clinical perspective, an important implication of these findings is that different antiresorptive agents cannot be compared on the basis of BMD endpoint trials (Boonen et al, 2004b).

FRACTURE PREVENTION

When licensing osteoporosis therapies, the regulatory authorities distinguish between prevention of bone loss in postmenopausal women with osteopenia and increased risk of fracture, and treatment to reduce fracture risk in postmenopausal women with osteoporosis (RCP/BATS, 2000). However, current UK guidelines advise that in clinical practice the aim should be to prevent an osteoporosis-related fracture whether or not a fragility fracture has already occurred (RCP/BATS, 2000).

All patients should receive advice on appropriate lifestyle measures to protect their bones, and excellent information leaflets can be obtained from the National Osteoporosis Society (see *useful address*). These measures should include a balanced diet with adequate intake of calcium and vitamin D, together with physical activity. Restoring calcium balance is particularly important: when given in appropriate doses, calcium and vitamin D have been shown to be pharmacologically active (particularly in patients with dietary deficiencies), safe and effective for the prevention of osteoporotic fractures (Boonen et al, 2004d). Calcium and vitamin D are now generally considered an essential, but not sufficient, component of an integrated management strategy for the prevention and treatment of osteoporosis in patients with dietary insufficiencies, although maximal benefit in terms of fracture prevention requires the addition of antiresorptive therapy.

CHOICE OF TREATMENT

Patients with a history of fragility fracture and/or strong risk factors for fracture will require specific pharmaceutical treatment to prevent osteoporosis-related fractures. There are now a number of effective therapies that have been shown in clinical trials to reduce the risk of fracture (Delmas, 2002); these fracture risk reductions have been documented on top of the benefit already provided by calcium and vitamin D. Osteoporosis is a chronic disease, so it is also important to choose a well-tolerated treatment and to provide ongoing support and follow-up to help patients adhere to their treatment in the long term.

Speed of onset of action is another important consideration when choosing an osteoporosis therapy. In an unpublished survey of UK GPs, more than half of respondents expected a patient to suffer a second fracture within 1 year, and two-thirds stated that they were not prepared to wait more than 6 months after initiating treatment for their patients to be protected from fracture. This may well be because of the GPs' real-life experience, since 45% reported that some of their patients had suffered a second osteoporosis-related fracture within 12 months of their first. This experience is in line with published data in untreated postmenopausal women with vertebral fractures showing that the proportion of individuals who suffer a new vertebral fracture within 1 year is approximately 20% or 1 in 5 (Lindsay et al, 2001). The risk of these women sustaining any type of osteoporotic fracture within 1 year is 1 in 4. These data change the paradigm for osteoporosis which has long been considered a slowly progressing disease. Once a vertebral fracture occurs, osteoporosis can progress quite quickly.

Fast-acting treatment is of particular importance for patients taking glucocorticoids, as fracture risk increases rapidly after the onset of treatment with glucocorticoids – within 6 months. Fractures also occur at a higher BMD in glucocorticoid-induced osteoporosis than in post-menopausal osteoporosis, so measurement of BMD is not required in high-risk patients (e.g. those over 65 years of age) before prescription (Bone and Tooth Society/National Osteoporosis Society/Royal College of Physicians (BATS/NOS/RCP), 2002).

RISEDRONATE

Risedronate is a pyridinyl bisphosphonate indicated for the treatment of postmenopausal osteoporosis and for the prevention of osteoporosis including corticosteroid-induced osteoporosis in postmenopausal women (British Medical Association and Royal Pharmaceutical Society of Great Britain, 2003). In women with postmenopausal osteoporosis, risedronate 5 mg daily provides significant protection from vertebral and non-vertebral fractures in just 6 months

(Harrington et al, 2004; Roux et al, 2004) – a more rapid onset of action than any other currently licensed therapy. The risedronate 35 mg once a week schedule is therapeutically equivalent to the 5 mg daily dose in postmenopausal women.

Like other bisphosphonates, risedronate's mode of action depends on inhibition of bone resorption, achieved by reducing the recruitment and activity and increasing the apoptosis of osteoclasts (Boonen et al, 2004b). This slows remodelling and enables bone formation to exceed bone resorption, leading to refilling of the remodelling space, more complete bone mineralization, and increased BMD overall (Follin and Hansen, 2003) and at the lumbar spine, femoral neck, femoral trochanter and midshaft of the radius compared with placebo (Harris et al, 1999).

Risedronate to protect bone quality

Although the risk of fracture almost doubles for each SD reduction in BMD on DXA (Kanis, 2002), this investigation does not provide a total picture of bone strength (NIH Consensus Development Panel, 2001) because DXA measures only the quantity of bone based on its size and mineral density. The strength of the skeleton also depends on the quality of the intricate trabecular microarchitecture inside the outer or cortical shell (*Figure 1*), and risedronate's rapid onset of efficacy is thought to be a result of its positive effects on bone architecture as well as on bone mass and bone quality.

Within bone, trabeculae interconnect vertically and horizontally to form a three-dimensional matrix that strengthens the skeleton in the same way that interconnecting steel rods reinforce concrete. In patients with osteoporosis, accelerated bone turnover leads to thinning or disappearance of the trabeculae, resulting in gaps in the skeleton's microarchitecture and an increased risk of fracture. In three-dimensional microcomputed tomography studies of iliac crest bone biopsy samples from postmenopausal women with established osteoporosis, 12 months treatment with risedronate 5 mg daily protected bone architecture from loss of connectivity. In contrast, there was a 20.3% decrease in bone volume, a 13.5% decrease in trabecular number, a 13.1% decrease in trabecular separation, and an 86.2% in marrow star volume (a measure of porosity) compared with baseline in women receiving placebo. These changes in bone microarchitecture in the placebo group were accompanied by a decrease from baseline of 3.3% in BMD at the lumbar spine (Dufresne et al, 2003).

There is also evidence from bone biopsy studies that 3 years' treatment with risedronate preserves bone quality in postmenopausal women with osteoporosis. In women receiving risedronate 5 mg there was no significant effect on mineral crystallinity or collagen cross-link, while there was a statistically significant decrease in bone quality in women who had been treated with placebo, as measured by these markers (Paschalis and Phipps, 2003; Borah et al, 2004).

Risedronate to reduce fracture risk

In postmenopausal women with low BMD, prevention of the first vertebral fracture is an important clinical objective because, as discussed above, women who have experienced vertebral fracture are at increased risk of future vertebral and non-vertebral fractures.

Clinical evidence suggests that, of the available bisphosphonates, risedronate offers the fastest protection from vertebral and non-vertebral fractures. In postmenopausal women with ≥1 pre-existing vertebral fracture, risedronate provides significant protection from vertebral fracture in just 6 months, with a 69% reduction seen at 1 year (Roux et al, 2004) (*Figure 2*). This early onset of action (significant at the 6-month time point) occurs in the presence of relatively small changes in BMD, providing further evidence that increases in BMD only provide a minor contribution to the antifracture efficacy.

Risedronate can also be used in postmenopausal women with low BMD (a DXA-assessed T-score below -2.5) but no pre-existing fractures. In an

Figure 1. Elements of bone quality.

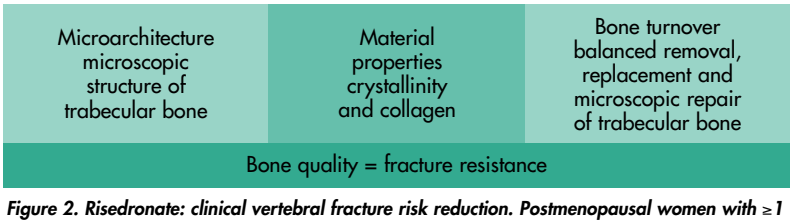
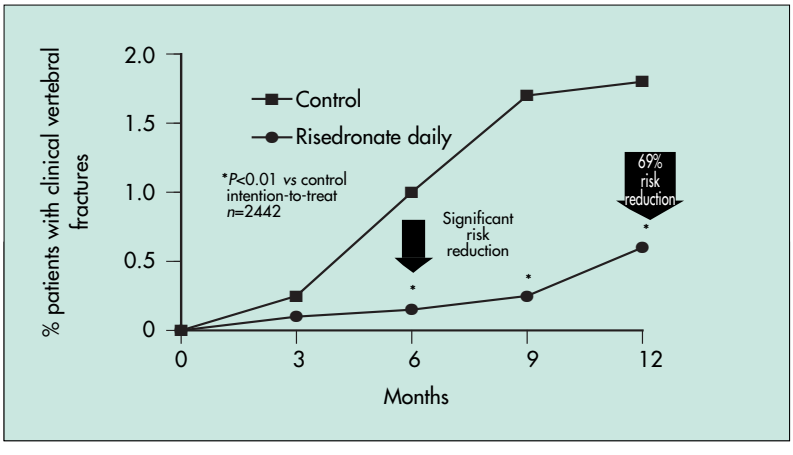


Figure 2. Risedronate: clinical vertebral fracture risk reduction. Postmenopausal women with ≥1 pre-existing vertebral fracture. Control = calcium and vitamin D as required by study protocol. Combined analysis of two registration studies. From Roux et al (2004).



analysis of postmenopausal women who had low lumbar spine BMD and no vertebral fractures at baseline, risedronate provided a 70% reduction in vertebral fracture at 3 years (Heaney et al, 2002).

Hip fractures have been described as the 'international barometer' of osteoporosis (Cummings and Melton, 2002). They cost more to repair and cause more disability than any other osteoporosis-related fracture, and they are almost always treated in hospital (Cummings and Melton, 2002). Prevention of hip fracture is therefore an extremely important clinical aim.

In a study of 5445 women aged 70–79 years with osteoporosis included in a double-blind, randomized clinical trial, the incidence of hip fracture with risedronate 5 mg daily was 1.9% compared with 3.2% in the placebo group, giving a risk reduction of 60% (McClung et al, 2001). A risk reduction of 46% was also demonstrated in patients aged 70–100 years at 3 years (Procter & Gamble Pharmaceuticals, 2002). This efficacy in elderly patients is also supported by data that show that risedronate significantly reduced the risk of new vertebral fractures by 65% at 1 year in elderly patients aged 75 and even 80 years or older (Boonen et al, 2004c).

These findings provided the first evidence that, even in patients 80 years of age or older, reducing bone resorption rate remains an effective osteoporosis treatment strategy. In these very old patients, risedronate is currently the only antiresorptive agent with documented antifracture efficacy. After 1 year, the risk of new vertebral fractures in the risedronate group was reduced by 81% compared with placebo. The number of women over 80 years of age who needed to be treated to prevent one new vertebral fracture after 1 year was 12. This early onset of efficacy was consistent across the clinical programmes, and antifracture efficacy was confirmed over 3 years. Risedronate was well tolerated, with a safety profile comparable to placebo.

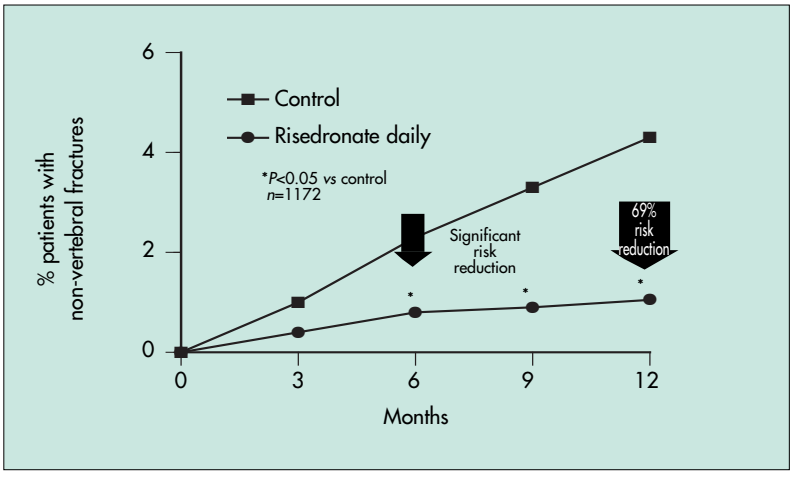
Risedronate also significantly reduces the risk of non-vertebral fracture in 6 months, in postmenopausal women with low BMD with or without a pre-existing vertebral fracture (McClung et al, 1997; Harrington et al, 2004), again giving 69% risk reduction after 1 year (*Figure 3*). In line with these trial results, results of an observational study evaluating the antifracture efficacy of osteoporosis therapies showed that postmenopausal women receiving risedronate sodium 5 mg daily had a significantly lower risk of developing non-vertebral fractures within the first 6 months of therapy compared to a control group of patients taking nasal calcitonin. Conversely, patients who received alendronate 10 mg daily or 70 mg weekly showed no significant reduction in the risk of developing non-vertebral fractures compared to the same control group (Watts and Worley, 2003).

Although these observational data should be interpreted cautiously and cannot substitute for a prospective, head-to-head comparative trial, they point again to the consistency of the early efficacy data obtained with risedronate. Non-vertebral fracture reduction within the first 6 months has not been documented with any of the other available bisphosphonates; however, in the FOSIT study alendronate 10 mg/day was shown to reduce non-vertebral fracture risk within 12 months (Pols et al, 1999).

The benefits of risedronate continue in long-term follow-up of postmenopausal women with osteoporosis enrolled in clinical trials. In a double-blind 2-year extension of a 3-year study, fracture efficacy compared to placebo was consistent with that observed in the first 3 years of treatment. In years 4 and 5 the risk of new vertebral fractures was significantly (95% confidence interval 19–79%, P=0.01) reduced by 59% compared with a 49% reduction in the first 3 years, providing randomized, double-blind evidence for sustained efficacy over 5 years (Sorensen et al, 2003a), longer than with any other bisphosphonate. Data suggest that risedronate 5 mg daily continues to protect against fractures in up to 7 years of treatment (Sorensen et al, 2003b).

Finally, risedronate also protects the skeleton against the effects of oral corticosteroids, taken in England and Wales by nearly 1% of the general adult population and 2.5% of those aged 70–79 years (BATS/NOS/RCP, 2002). In postmenopausal women receiving moderate to high-

Figure 3. Risedronate: non-vertebral fracture risk reduction (osteoporotic fractures of the hip, wrist, humerus, pelvis, clavicle and leg). Postmenopausal women with low bone mineral density, with or without pre-existing vertebral fracture. Control = calcium and vitamin D as required by study protocol. Combined analysis of four registration studies. From Harrington et al (2004).



dose corticosteroids (equivalent to ≥7.5 mg prednisolone daily), risedronate significantly increased BMD at the spine and hip and reduced the risk of vertebral fracture by 70% compared with placebo (Wallach et al, 2000). These benefits were achieved within 1 year of initiation of treatment with risedronate, an important consideration since fracture risk increases rapidly after starting corticosteroid therapy (BATS/NOS/RCP, 2002). Guidelines on the treatment of glucocorticoid-induced osteoporosis recommend that patients at high risk, such as those over 65 years of age or those with a prior fragility fracture, should commence bone-protective therapy at the time of starting glucocorticoid treatment to prevent fractures (BATS/NOS/RCP, 2002).

TOLERABILITY AND COMPLIANCE

Successful treatment with bisphosphonates requires that patients comply with their therapeutic regimen. This can sometimes be difficult, as there is no positive benefit or visible outcome that patients can identify with in relation to their treatment, as it is intended to work as a prophylaxis against fractures. Therefore clinicians must select appropriate therapies that will not further inhibit patient compliance and concordance.

While the most commonly reported side-effect of the bisphosphonate class is gastrointestinal (GI) upset (British Medical Association and Royal Pharmaceutical Society of Great Britain, 2003), risedronate has comparable tolerability to placebo, even in patients at risk of suffering GI side effects (Taggart et al, 2002). In this regard, it is important to note that the alendronate trials which have been published – including the once-a-week trial – used a variety of upper GI exclusion criteria, whereas the risedronate studies did not. Despite the fact that more than 20% of the women included in the (double-blind) risedronate studies were on proton pump inhibitors at some time, no safety concerns emerged. A study showed that alendronate patients demonstrated a 42% higher risk of incurring a GI event in the first 4 months of therapy compared to patients taking risedronate, adjusting for pre-existing GI conditions and age (Worley et al, 2003). In this regard, it should be noted that, while both drugs are potent nitrogen-containing bisphosphonates, alendronate is an aminobisphosphonate (like pamidronate), whereas risedronate is not.

Although some patients find it easy to remember to take a daily fasting dose of medication, this may be more of a challenge for others, especially if they are receiving regular treatment for co-morbid chronic disease. These patients can be prescribed a more convenient, once-weekly 35 mg dose of risedronate, which is as well tolerated as risedronate 5 mg daily. The once-weekly dosing has been shown to be therapeutically equivalent to risedronate 5 mg daily (Brown et al, 2002).

CONCLUSIONS

Osteoporosis is a chronic, progressive disease that rapidly reduces bone quality, and results in fragility fractures that are associated with premature morbidity and mortality in postmenopausal women. Patients therefore need an effective, fast-acting treatment that will protect their skeleton and reduce their risk of fracture. In randomized, double-blind clinical studies risedronate 5 mg daily compared to placebo significantly reduced the incidence of fracture at the hip, spine and non-vertebral sites, with a significant effect on vertebral and non-vertebral fractures within 6 months. This antifracture efficacy has been consistently documented across different trials, different types of osteoporosis, different age ranges and different degrees of osteoporosis.

In addition to risedronate's rapid-acting fracture protection, its GI safety profile – even in women with a history of or with active upper GI diseases – is a benefit for patients and could enhance treatment compliance. Evidence therefore supports the role of risedronate as a first-line treatment for the prevention of fractures in osteoporosis and corticosteroid-induced osteoporosis in postmenopausal women. HM

Dr S Boonen and Dr D Vanderschueren are Senior Clinical Investigators of the Fund for Scientific Research, Flanders, Belgium (F.W.O. Vlaanderen). Dr Boonen is holder of the Leuven University Chair for Metabolic Bone Diseases.
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KEY POINTS

- Osteoporosis is a major public health problem in the UK as in the rest of the world and is likely to become more common as the population ages.
- One in three women and one in 12 men aged over 50 years will sustain an osteoporosis-related fracture in their lifetime.
- Osteoporosis is a chronic, progressive disease, but bone strength can deteriorate rapidly, with one in five postmenopausal women who develop a vertebral fracture sustaining another fracture within 1 year.
- Patients require a fast-acting, efficacious, well-tolerated treatment such as risedronate.
- In clinical trials, risedronate significantly reduced the risk of both vertebral and non-vertebral fractures within 6 months in postmenopausal women.
- In clinical trials that did not exclude patients with active upper gastrointestinal diseases, the incidence of upper gastrointestinal adverse effects with risedronate was similar to that in patients receiving placebo, even in high-risk patients.
- Risedronate is available in two formulations: a daily dose of 5 mg and a convenient once-weekly 35 mg dosage.

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Useful address

National Osteoporosis Society

The National Osteoporosis Society is the leading professional and patient organization in the UK concerned with osteoporosis.

The National Osteoporosis Society
Camerton
Bath BA2 0PJ
Telephone 01761 471771 (general enquiries) Fax: 01761 471104
Helpline: 0845 4500230 (medical queries)
E-mail: info@nos.org.uk Website: www.nos.org.uk