Risedronate: a new bisphosphonate on the block

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A new third generation bisphosphonate, risedronate (Actonel), is now available, joining two existing members of this therapeutic class. This article describes the evidence supporting the use of risedronate in osteoporosis and Paget's disease.

What do we know about risedronate?

Risedronate, a third-generation bisphosphonate, has potent antiresorptive activity in bone and is therefore of interest in treating metabolic bone disorders. Its efficacy has been evaluated extensively in osteoporosis (postmenopausal and corticosteroid-induced) and Paget's disease.

Postmenopausal osteoporosis

The ultimate test of a new treatment for osteoporosis is a reduction in fracture rate. Risedronate has been shown to significantly reduce fracture rates of both the spine and hip in postmenopausal women with osteoporosis (Figure).

In 1999, the results of a three-year study of risedronate in postmenopausal osteoporosis were published.[1] This study involved over 2400 women, all of whom had at least one vertebral fracture at baseline. After 12 months, 16% of patients receiving risedronate had suffered a new vertebral fracture (compared with 46% on placebo), and the magnitude of this benefit was maintained after three years of therapy. The treatment also resulted in a significant rise in bone mineral density (BMD) and fall in markers of bone resorption. After three years of treatment, the risk of nonvertebral fractures was significantly reduced (33% receiving risedronate had new nonvertebral fractures compared with 52% on placebo).

The following year, these results were confirmed in a randomised study conducted in Europe and Australia that involved more than 1200 postmenopausal women with two or more vertebral fractures.[2] Treatment reduced the risk of new vertebral fracture by 49% over a three-year period (18.1% of patients suffered a new vertebral fracture compared with 29% taking placebo); a positive effect on BMD was observed and the treatment was well tolerated. (The risk of nonvertebral fractures was reduced by 33% compared with placebo, but this result did not achieve statistical significance because of the smaller number of patients involved in this study.)

The effect of risedronate on the risk of hip fracture was observed in the first study to evaluate prospectively the effect of antiresorptive therapy on hip fractures as a primary outcome.[3] This three-year, placebo-controlled trial involved more than 9000 patients over 70 years of age. Risedronate was associated with a 40% reduction in the risk of hip fracture in women aged between 70 and 79 years who had osteoporosis defined either by a femoral neck BMD T score less than -4 or by a T score less than -3 in the presence of at least one nonskeletal risk factor. However, in women aged over 80 years in whom a diagnosis of osteoporosis was based on nonskeletal risk factors (not BMD), treatment was not associated with a reduction in hip fracture. These results confirm that risedronate reduces hip fracture in elderly postmenopausal women with confirmed osteoporosis (i.e. a T score less than -3), and that BMD measurements – rather than clinical risk factors – are of value in identifying patients in whom therapy is indicated.

Corticosteroid-induced osteoporosis

Risedronate has been evaluated in the prevention and treatment of glucocorticoid-induced osteoporosis.[4] In a one-year, placebo-controlled trial in men and women who had initiated treatment with at least 7.5 mg prednisolone daily, risedronate protected against loss of cortical and trabecular bone. There was also a trend towards a reduction in vertebral fractures. In another study of postmenopausal women with rheumatoid arthritis treated with prednisolone, risedronate

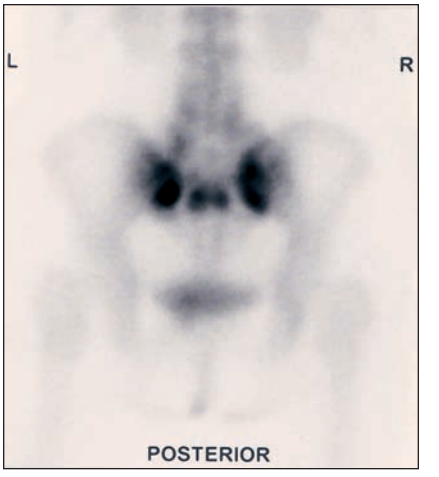

Figure. A nuclear bone scan showing a sacral insufficiency fracture (classic H sign) and a fracture of the left pubic ramus due to osteoporosis.

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preserved bone mass over the two-year period of the study, while patients receiving placebo had a significant loss of bone.[5]

Paget's disease

Risedronate has been compared directly with etidronate in the treatment of Paget's disease. In a prospective, randomised, double-blind study, 62 patients receiving risedronate (30 mg daily for two months) and 61 patients receiving etidronate (400 mg daily for six months) were monitored for 12 to 18 months.[6] Risedronate offered a more rapid and longer lasting response than etidronate, with a higher percentage of patients achieving normalisation of biochemical markers. Both risedronate and etidronate were well tolerated, and no difference in side effects was observed between the two therapies.

Prescribing risedronate

Indications

Risedronate is the only anti-osteoporotic treatment that has been shown to reduce hip fracture in a primary prevention setting. It is PBS-listed and can be prescribed (on authority) for postmenopausal osteoporosis in patients with fracture due to minimal trauma. Risedronate is more potent than etidronate and has similar efficacy data to alendronate; however, it has not been compared head-to-head with any other bisphosphonate in the treatment of osteoporosis.

Risedronate is indicated for the prevention and treatment of corticosteroid-induced osteoporosis. However, the treatment does not have a PBS listing for prescription for this indication.

Risedronate can also be prescribed for symptomatic Paget's disease (PBS listed, on authority). It has superior efficacy to etidronate in Paget's disease, but has not been directly compared with pamidronate, alendronate or tiludronate. Of the oral bisphosphonates available for Paget's disease, risedronate has the advantage of having the shortest course.

It is available in two strengths:

- 5 mg tablets, which are indicated for postmenopausal osteoporosis, glucocorticoid-induced osteoporosis and preservation of BMD in patients on long term corticosteroid therapy
- 30 mg tablets, which are indicated for Paget's disease (a two-month course).

It must be remembered that risedronate treatment must be accompanied by an adequate intake of calcium. Supplemental vitamin D may be required if the patient is deficient in this vitamin.

Interactions

The interactions of risedronate are similar to those of other bisphosphonates. Calcium, antacids and iron tablets (if used) should be taken at a different time of the day. Risedronate is a category B3 drug (i.e. it has not been studied in pregnancy); in addition, it is not known whether the drug is excreted in milk and so it is best avoided during lactation.

Side effects

In the published clinical trials to date, no differences in the incidence of upper gastrointestinal adverse events have been observed compared with placebo. Some studies included patients with a history of upper gastrointestinal disorders, but it must be remembered that patients in clinical trials are much more likely to conform to correct drug administration. In a short term endoscopic study of 515 postmenopausal women, risedronate resulted in a significantly lower incidence of upper gastrointestinal ulcers than alendronate. Whether these results translate into better gastrointestinal tolerance 'in the field' will come to light with post-marketing surveillance. It seems likely that risedronate will result in a lower incidence of gastrointestinal side effects than alendronate, but patients will need to adhere strictly to the dosing regimen. MT

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