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Risedronate

A Review of its Pharmacological Properties and Clinical Use in Resorptive Bone Disease

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Data Selection

Sources: Medical literature published in any language since 1983 on risedronate, identified using AdisBase (a proprietary database of Adis International, Auckland, New Zealand), Medline and EMBASE. Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: AdisBase search terms were 'risedronate' or 'NE-58095'. Medline search terms were 'risedronate' or 'NE-58095'. EMBASE search terms were 'risedronate' or 'NE 58095'. Searches were last updated 4 Apr 2001.

Selection: Studies in patients with postmenopausal or glucocorticoid-induced osteoporosis or Paget's disease who received risedronate. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Risedronate, bisphosphonates, resorptive bone disease, osteoporosis, postmenopausal, glucocorticoid-induced, Paget's disease, pharmacodynamics, pharmacokinetics, therapeutic use, tolerability, dosage and administration, review.

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Summary

Abstract

Risedronate is a novel orally administered pyridinyl bisphosphonate indicated for the prevention or treatment of postmenopausal and glucocorticoid-induced osteoporosis and Paget's disease. The drug reduces bone turnover and decreases resorption chiefly through osteoclastic effects, with no undesirable effects on cortical porosity or thickness or on cancellous bone volume.

Four randomised, double-blind trials have been carried out in 4873 patients with postmenopausal osteoporosis. In 2 of these studies, the primary end-point of vertebral fracture incidence was reduced by risedronate 5mg once daily by up to 65 and 49% relative to placebo after 1 and 3 years, respectively. Across all 4 trials, risedronate improved lumbar spine, femoral neck and femoral trochanter bone mineral density (BMD) statistically significantly relative to placebo. The drug also prevented bone loss in a study in 383 women with recent menopause, and reduced the risk of hip fracture in elderly women with confirmed osteoporosis in a trial involving a total of 9331 patients. Risedronate 5 mg/day plus estrogen has been shown to be superior to estrogen alone in a 12-month double-blind study in 524 women with at least 1-year's history of menopause.

Two randomised, double-blind and placebo-controlled 12-month studies in a total of 518 patients have shown risedronate 5 mg/day to prevent or reverse bone loss in patients receiving glucocorticoid therapy.

Risedronate 30 mg/day was associated with statistically significant reductions in mean serum levels of alkaline phosphatase (ALP) in noncomparative studies in patients with Paget's disease. ALP normalisation rates ranged from 53.8 to 65% across two 84-day treatment cycles in 2 of these trials in 180 patients. In a randomised, double-blind study in 123 patients, risedronate 30 mg/day for 2 months evoked significantly greater serum ALP responses than etidronate 400 mg/day for 6 months.

The overall tolerability profile of risedronate was similar to that of placebo in clinical studies, with no evidence of acute-phase reactions or mineralisation defects, or excess incidence of upper GI lesions, in patients receiving the drug.

Conclusions: Risedronate is an effective and well tolerated novel bisphosphonate that is suitable for first-line therapy in Paget's disease. The rapid and sustained reductions in vertebral fracture incidence and BMD changes seen in patients with postmenopausal and glucocorticoid-induced osteoporosis indicate the drug to be a valuable treatment option with first-line potential, particularly in patients for whom hormonal therapy is inappropriate. The effects of the drug on hip fracture incidence in elderly women with confirmed osteoporosis point to a particular role in older patients, or those with more advanced disease.

Pharmacological Profile

Risedronate inhibits bone resorption by interfering with the recruitment and activity of osteoclasts. As with other bisphosphonates, the drug is believed also to inhibit osteoclastic adhesion to mineralised bone matrix and to shorten the osteoclastic life span.

Risedronate 5 mg/day (all dosages quoted are oral unless stated otherwise) reduces bone turnover as shown consistently in clinical studies in postmenopausal women and patients with Paget's disease by statistically significant reductions relative to placebo in serum levels of bone-specific ALP. Maximal reductions are typically obtained after 6 months' treatment and are accompanied by reductions in urinary markers of bone resorption (e.g. N-telopeptide and deoxypyridinoline).

Histomorphometric analysis in patients receiving risedronate for corticoste-

roid-induced osteoporosis showed decreased resorption depth with unchanged rates of resorption (resulting in a net decrease in bone resorption) with the drug. There were no undesirable effects on cortical porosity or thickness or on cancellous bone volume. Trabecular width and rates of mineralisation remained unchanged, and bone turnover decreased, in patients with skeletal deterioration caused by multiple myeloma who received risedronate.

Risedronate undergoes rapid absorption and shows a dose-proportional pharmacokinetic profile after oral administration. Mean peak serum concentrations (C_{max}) of risedronate were 0.41, 0.94 and 5.1 μg/L after single doses of 1.5, 5 and 30mg, respectively, in healthy volunteers. Mean times to C_{max} ranged from 0.81 to 0.87 hours. GI absorption of the drug is impaired by the presence of food, and by calcium-, magnesium- or aluminium-containing compounds.

The volume of distribution at steady state of risedronate was 6.3 L/kg after intravenous administration in 1 study. The terminal elimination half-life is long (480 hours), and the drug is excreted unchanged largely via the kidneys, with renal clearance (CL_R) accounting for 87% of total clearance. CL_R and volume of distribution are related linearly to creatinine clearance (CL_{CR}). Risedronate is known not to interfere with the function of hepatic microsomal cytochrome P450 enzymes.

Therapeutic Use

Postmenopausal Osteoporosis. Following the demonstration of efficacy relative to placebo of risedronate in women with postmenopausal osteoporosis in phase II studies, the drug was compared with placebo in a series of 6 randomised, double-blind phase III clinical trials. Four of these studies involved risedronate treatment of 4873 patients with low bone mass; vertebral fracture incidence was measured as the primary end-point in 2 of these, which involved women with established osteoporosis at baseline. The other studies focused on prevention of osteoporosis (i.e. maintenance of baseline bone mass) in women with recent menopause, and reduction of risk of hip fracture in elderly women.

Statistically significant improvements relative to placebo in vertebral fracture incidence and/or in lumbar spine, femoral neck and femoral trochanter BMD were seen consistently with risedronate 5mg once daily. In the 2 vertebral fracture studies, significant (61 and 65%; $p \leq 0.001$ *vs* placebo) reductions in vertebral fracture risk were evident with risedronate treatment by the end of the first year. The risk of new fractures was reduced over 3 years by 41 ($p = 0.003$) and 49% ($p < 0.001$) relative to placebo. There were also substantial (39 and 33%) reductions in the risk of nonvertebral fracture (the first of these 2 results was also statistically significant).

Statistically significant improvements relative to placebo in BMD were noted from 6 months onwards with risedronate 5 mg/day in the vertebral fracture studies. After 3 years, mean treatment differences of 5.9, 6.4, 3.1 and 2.1% were reported for the lumbar spine, femoral trochanter, femoral neck and midshaft radius, respectively (all $p < 0.001$ *vs* placebo), in 1 trial.

In the 2 studies in patients with low baseline bone mass in which BMD was the primary end-point, mean lumbar spine BMD increased from baseline by 4.1% over 2 years ($p < 0.001$ *vs* placebo) in 1 trial and by 4.7% over 18 months ($p < 0.05$ *vs* placebo) in the other with risedronate 5 mg/day.

Statistically significant increases relative to both baseline and placebo with risedronate 5 mg/day in spinal and hip BMD were reported from as early as 3

months after starting treatment in a preliminary report of the bone loss prevention study in 383 women with a history of recent (6 to 36 months) menopause.

Risedronate treatment reduced the risk of the primary end-point of hip fracture in elderly women with established osteoporosis as confirmed by low BMD in a 3-year study in which 9331 patients were randomised within 2 strata to risedronate 2.5 or 5mg daily or placebo. In group 1 (patients aged 70 to 79 years with confirmed osteoporosis at baseline), hip fracture incidences were 1.9% with risedronate and 3.2% with placebo (relative risk 0.6; $p = 0.009$). The relative risk of hip fracture associated with risedronate treatment in 1703 women in group 1 with evidence of at least 1 vertebral fracture at baseline was 0.4 ($p = 0.003$ *vs* placebo). The corresponding relative risk in 2648 group 1 women with no history of vertebral fracture was 0.6 ($p = 0.14$).

There was no significant effect of risedronate treatment on hip fracture risk in group 2 (patients aged 80 years and over, most of whom were recruited on the basis of presence of clinical risk factors only): hip fracture incidences of 4.2 and 5.1% were reported for the risedronate and placebo groups, respectively ($p = 0.35$). Further analysis suggested that the majority of patients in group 2 did not have osteoporosis. Overall, incidences of hip fracture were 2.8% in all women who received risedronate and 3.9% in those who received placebo in this study (relative risk 0.7; $p = 0.02$).

BMD measurements indicated superiority of risedronate 5 mg/day plus estrogen therapy ($n = 261$) over estrogen alone ($n = 263$) in a 12-month double-blind placebo-controlled study in women with at least 1 year's history of menopause. Improvements with risedronate plus estrogen were significantly greater than those with estrogen alone at 6 months for the lumbar spine and at 12 months for the femoral neck and midshaft radius.

Glucocorticoid-Induced Osteoporosis. In a randomised, double-blind, placebo-controlled phase III study in 228 patients starting glucocorticoid therapy, lumbar spine, femoral neck and femoral trochanter BMD decreased from baseline by around 3% over 12 months in patients receiving placebo. In contrast, BMD was maintained at the lumbar spine and femoral neck, and was increased at the femoral trochanter, with risedronate 5 mg/day. Least squares mean differences from placebo were 3.8, 4.1 and 4.6%, respectively (all $p < 0.001$). BMD was also maintained in recipients of risedronate 2.5 mg/day, but effects were less marked than with the 5 mg/day dosage. Distal and midshaft radius BMD did not change significantly relative to baseline in any group, and there were no statistically significant differences from placebo with either active treatment.

Risedronate 5 mg/day significantly increased BMD relative to placebo at the lumbar spine and the femoral neck and trochanter in 290 patients on glucocorticoid therapy and with low BMD at baseline in another 12-month randomised double-blind study.

Although neither trial was designed to detect differences between treatment groups with respect to incidence of vertebral fracture, combined results from the 2 studies nevertheless indicated an encouraging overall 70% reduction in this end-point ($p = 0.01$ *vs* placebo).

Paget's Disease. In 2 noncomparative studies in which risedronate 30mg was given once daily for 84 days (with additional 112-day follow-up) in 20 and 160 patients with moderate to severe Paget's disease, mean serum ALP levels were reduced from the first post-baseline measurement (day 29) onwards ($p < 0.001$

vs baseline for both studies). Patients whose serum ALP levels did not normalise received a second cycle of treatment; ALP normalisation rates were 65 and 53.8% across both cycles in these 2 studies. All patients were free from pain by day 56 of the second cycle in the smaller study; in the larger trial, 42% of 154 evaluable patients were pain-free on day 196 ($p < 0.001$ *vs* baseline).

Risedronate 30mg once daily for 2 months has been compared with etidronate 400mg daily for 6 months in 123 patients with Paget's disease in a randomised double-blind trial with 12- and 18-month follow-up. Both drugs were associated with reductions from baseline ($p < 0.01$) in serum levels of ALP from 1 month onwards, but risedronate evoked greater responses than etidronate ($p < 0.001$ between treatments). Maximum mean changes from baseline in ALP were seen at 6 months and were 69 and 33% for risedronate and etidronate, respectively. Biochemical remission was achieved in 77 and 11% of patients by month 6 ($p < 0.001$). After 18 months, 53 and 14% of evaluable risedronate and etidronate recipients, respectively, had serum ALP levels within the normal range. There was no statistically significant difference between treatments in mean pain scores, and no significant improvements in other quality-of-life measures (Short Form Health Survey) were reported with either drug.

Tolerability

Adverse event reporting rates were 92.1% with risedronate 5mg daily and 92.8% with placebo in patients below 80 years of age in an analysis of tolerability results from 10 068 individuals included in an assessment of 15 066 patients enrolled in placebo-controlled clinical studies. Corresponding rates in patients aged 80 years and over were 87.9 and 88.3%. Withdrawal rates were also similar between treatment groups for both age categories.

According to collated data from over 5700 patients in phase III osteoporosis studies, overall incidences of serious adverse events were 24.9% with placebo and 26.3% with risedronate 5 mg/day; rates of withdrawal from treatment were 14.4 and 13.5%, respectively. Risedronate 10 to 30 mg/day was well tolerated by 392 patients with Paget's disease who participated in clinical trials. Similar tolerability profiles between treatment groups were apparent in a clinical trial comparing risedronate 30 mg/day with etidronate 400 mg/day, with the most commonly reported adverse events possibly or probably related to study medication (both drugs) being arthralgia, diarrhoea, headache, abdominal pain and skin rash.

Tolerability data from the analysis of 15 066 patients randomised in clinical studies to risedronate or placebo treatment have shown no excess incidence relative to placebo of upper GI lesions in patients receiving risedronate 5 mg/day. Similarity between groups was maintained in patients with a history of upper GI disease, those receiving NSAID or aspirin treatment, and those using histamine H_2-receptor antagonists or proton pump inhibitors.

Rates of gastric ulceration after endoscopic examination on days 8 and 15 in a recent 2-week study in 448 healthy postmenopausal women were 4.1% with risedronate 5 mg/day and 13.2% with alendronate 10 mg/day ($p < 0.001$). Another study in 235 patients has shown similar mean gastric erosion scores after 28 days' therapy with risedronate 30 mg/day or alendronate 40 mg/day. There have been no reports of any acute-phase reactions, age-related increases in adverse event reporting or mineralisation defects in patients receiving risedronate therapy.

Dosage and Administration

Risedronate tablets should be taken once daily at least 30 minutes before the first meal or drink (other than water) of the day, and should be swallowed with a full

glass of water by patients in an upright position. Patients should not lie down for at least 30 minutes after taking risedronate. Supplemental calcium and calciferol should be prescribed for those whose dietary intake is inadequate.

The recommended daily dosage of risedronate for the prevention or treatment of postmenopausal and glucocorticoid-induced osteoporosis is 5mg. Patients with Paget's disease should receive 30mg daily for 2 months, with a second course after an additional 2-month treatment-free observation period if serum ALP levels do not normalise or disease relapse is seen.

There are no data on the use of risedronate in pregnant or nursing women. No dosage adjustment is necessary in elderly patients or in those with mild to moderate renal impairment ($CL_{CR} \geq 1.8$ L/h). The drug is not recommended in patients with CL_{CR} below 1.8 L/h, however.

1. Bone Physiology and the Bisphosphonates

Bone tissue incorporates a network of tiny anastomosing canals and spaces containing blood vessels, lymphatic tissue and bone cells. Around these canals and spaces is formed (in scale-like layers or 'lamellae') a rigid intercellular substance composed of a network of collagenous fibres that becomes impregnated with mineral salts, notably calcium phosphate and calcium carbonate.[1]

In addition to its structural function, the skeleton also serves as the body's store of calcium, a constant level of which in blood and tissue fluid is necessary for physiological processes including blood coagulation, muscular activity and heart action. Bone therefore acts as a repository for excess calcium, and provides a store from which deficits may be corrected when necessary.[1]

Bone is a living tissue that is in a state of continuous turnover and renewal (the bone remodelling cycle). This process allows the skeleton to respond to changing physiological demands and makes possible the repair of microstructural defects. The 3 types of bone cell that participate in this process, osteoblasts, osteocytes and osteoclasts, are found beneath the periosteum (the supportive membrane covering the bone) on the surface of growing bones and in developmental or ossification areas within the bones. Osteoclasts are multinucleated cells of the monocyte/macrophage lineage that resorb bone to leave behind shallow pits on the surface of the trabecular plates within bone or canals in cortical bone tissue. Their activity is coupled to that of osteoblasts, which synthesise new bone matrix (osteoid, which subsequently calcifies or 'mineralises') to fill in the defects left by the osteoclasts. Osteocytes are mature osteoblasts that become trapped by mineralisation. A locus of osteoclastic/osteoblastic activity is known as a bone remodelling unit, and the total activity of these units over the entire skeleton determines overall bone turnover.[1,2]

Net bone formation exceeds resorption during growth and development, and peak bone mass is achieved by the age of 30 years. Balanced bone turnover thereafter should ideally result in neither net gain nor loss of bone mass, although small losses are not abnormal.[2] The balance achieved by the bone remodelling cycle may be disrupted, however, by a number of disorders associated with inappropriate osteoclastic activity and accelerated bone turnover. These include most notably osteoporosis (associated with menopausal hormonal changes in women or corticosteroid use), Paget's disease (a focal disorder characterised by uncontrolled increases in bone turnover) and cancer (in which osteolytic factors released by tumours or localised bone destruction by metastases may be involved).[3]

The bisphosphonates are synthetic analogues of pyrophosphoric acid (fig. 1), a naturally occurring inhibitor of bone resorption that prevents ectopic calcification and the aggregation and dissolution of

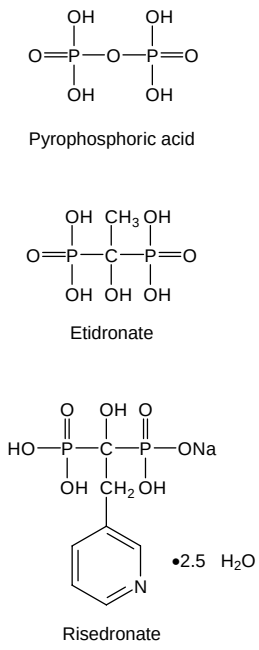

Fig. 1. Structural formulae of pyrophosphoric acid, etidronate and risedronate.

hydroxyapatite crystals, and inhibits the conversion of amorphous calcium phosphate into hydroxyapatite (reviewed by Johansen et al.[4]). Pyrophosphates found in blood, urine, saliva and synovial fluid may be involved in the regulation of bone turnover and the prevention of soft tissue calcification.[4]

The therapeutic usefulness of pyrophosphate compounds is limited by their rapid inactivation *in vivo* by pyrophosphatases.[5] The bisphosphonates, however, have structures based on a phosphorus-carbon-phosphorus chain with a double phosphonate group (instead of the phosphorus-oxygen-phosphorus sequence found in pyrophosphate). This renders them resistant to hydrolysis by pyrophosphatases and extends their biological duration of activity so that they are able to influence skeletal metabolism to a clinically useful extent.[6-8] As a class, the bisphosphonates have similar effects on bone crystals to the pyrophosphates, but their action appears to be more complex than the simple physicochemical interference seen with the latter.

Variation of functional groups on the central carbon atom of the basic bisphosphonate molecule has created a series of drugs, each with its own distinct pharmacological properties. The development of the first and structurally simplest of these agents, etidronate (fig. 1), marked the introduction of a novel approach to the management of resorptive bone disease (see review by Dunn et al.[9]). Since that time, researchers have sought improvements in potency and tolerability through alteration of the side chain attached to the central carbon atom of the basic bisphosphonate structure. The rationale behind the development of the novel orally administered pyridinyl bisphosphonate risedronate (fig. 1) lies in the gains in antiresorptive potency that appear to follow the attachment of a cyclic functional group to the central carbon atom of the bisphosphonate molecule.[10] This review discusses the pharmacology of risedronate and its use in the management of postmenopausal and corticosteroid-induced osteoporosis and Paget's disease.

2. Pharmacological Profile

2.1 Mechanism of Action

As with all the bisphosphonates, the exact mechanism of action of risedronate at the cellular level has not been fully clarified. Expressed in the simplest terms, however, all these drugs inhibit bone resorption by interfering with the recruitment and activity of osteoclasts.[11] This results in increased bone mineral density (BMD) and reduced risk of fracture. It should also be noted that the osteoclastic action of the bisphosphonates has been linked in the past to inhibition of mineralisation and subsequent osteomalacia in some patients.[12] These concerns appear, however, to be limited chiefly to etidronate, and newer bisphosphonates such as risedronate have been developed with the aim of optimising antiresorptive potency and eliminating any tendency to inhibit mineralisation. This issue is dealt with in more detail in section 4.

There is general agreement that the action of the bisphosphonates also involves inhibition of adhesion of osteoclasts to mineralised bone matrix and shortening of the osteoclastic life span. All these effects may be attributable to direct effects on the osteoclasts themselves and/or indirect effects through actions on cells (particularly osteoblasts) that modulate osteoclast production and behaviour. The reader is referred to the paper by Fleisch[11] for a full and detailed description of the postulated mechanisms of action of the bisphosphonates.

A large number of other cellular or biochemical effects of the bisphosphonates have been described (see Fleisch[11] for details), but the majority of these are unlikely to be involved in bone resorption. Induction of osteoclast apoptosis (programmed cell death) has been shown in *in vitro* and *in vivo* studies in mice, with risedronate being more active in this respect than pamidronate or clodronate.[13] Further data indicate that this effect is linked to inhibition of post-translational protein prenylation (modification) in the presence of nitrogen-containing bisphosphonates (such as risedronate, alendronate and ibandronate), and that enzymes of the mevalonate pathway or the prenyl protein transferases are the molecular targets of these drugs.[14]

2.2 Effects on Biochemical Markers of Bone Turnover

Disruption of bone remodelling in resorptive bone disease is associated with changes in a number of biochemical markers and products of collagen metabolism in blood and urine. Measurement of levels of these compounds before and after treatment in clinical studies therefore provides a useful indicator of probable mechanisms of action and clinical efficacy of agents used in metabolic bone disorders.

Reductions in rates of bone turnover during treatment with risedronate 5 mg/day have been shown by measurement of serum levels of bone-specific alkaline phosphatase (ALP) in randomised, placebo-controlled phase III studies in postmenopausal women (section 3.1).[15-17] Data from a subset of 775 patients from an originally randomised cohort of 2458 studied by Harris et al. showed median 35 and 12% reductions from baseline in serum levels of this marker after 6 months' treatment with risedronate and placebo, respectively (statistical significance not stated).[15] These reductions were sustained over 3 years, with median reductions from baseline of 33 and 7% for risedronate and placebo, respectively.

In a similarly designed study in 1226 postmenopausal patients, Reginster and colleagues reported a serum bone-specific ALP nadir after 6 months' treatment (median reduction from baseline of 37%) that was statistically significant ($p \leq 0.05$) relative to placebo (transient decrease of up to 10% over the first few months only).[17] The difference between groups was maintained for the 3 years of the study. In addition, serum bone-specific ALP levels were reduced after 24 months by a mean 22% relative to baseline by risedronate treatment ($p < 0.001$ *vs* 8% increase with placebo) in a study in 541 postmenopausal patients.[16] A significant difference between groups was evident from 3 months onwards.

Risedronate treatment has also been associated with significant reductions in serum levels of total and bone-specific ALP in studies in patients with Paget's disease.[18-21] Activities of these enzymes were used as primary end-points in these trials, however, and full details are therefore given in section 3.3.

The ratio of the levels of bone N-telopeptide relative to those of creatinine in urine was measured as a marker of bone resorption in 1 study,[16] and was reduced by a mean 44% from baseline after 24 months' risedronate treatment ($p < 0.01$ *vs* 11% decrease with placebo). In the other studies mentioned above,[15,17] median urinary deoxypyridinoline : creatinine ratios were reduced significantly relative to placebo by risedronate treatment (nadirs attained at 6 months in both trials).

2.3 Effects on Bone

Beneficial effects of risedronate on bone remodelling have been shown in studies carried out in animals (reviewed by Goa and Balfour[22]), and

histomorphometric data are now also available to show benefit in humans.

Iliac crest biopsies were obtained from 38 patients participating in a 12-month double-blind clinical study in which the effects of risedronate on corticosteroid-induced bone loss were being compared with those of placebo.[23] The effects of risedronate (5 mg/day) on bone histomorphometry (reported in an abstract) are summarised in figure 2; briefly, the drug decreased resorption depth without altering the resorption rate (the net effect being a decrease in bone resorption), with no deleterious effects on cortical porosity or thickness or on cancellous bone volume.

Histomorphometric analysis in 11 patients with skeletal deterioration caused by multiple myeloma who received risedronate 30 mg/day for 6 months showed significant reductions relative to baseline in activation frequency (52%; p = 0.02), numbers of osteoclasts (53%; p = 0.027) and erosion depth (20%; p = 0.002).[24] Osteoid parameters were also significantly decreased, whereas trabecular width and rate of mineralisation were unchanged. These findings were accompanied by decreases in bone turnover as shown by reductions in serum levels of ALP and osteocalcin and urinary levels of pyridinoline and deoxypyridinoline.

2.4 Pharmacokinetic Properties

After oral administration, risedronate is absorbed rapidly and shows a dose-proportional pharmacokinetic profile. Mean peak serum drug concentrations (C_{max}) in a study in 67 fasting healthy volunteers were 0.41, 0.94 and 5.1 μg/L after single doses of 2.5, 5 and 30mg (as film-coated tablets), respectively.[25] Mean times to C_{max} (t_{max}) ranged from 0.81 to 0.87 hours, and dose proportionality was confirmed by analysis of C_{max}, areas under serum drug concentration versus time curves (AUC) and amounts excreted in urine from baseline to infinity.[25] Comparison of film-coated tablet, oral solution and intravenous formulations of risedronate has shown the absolute oral bioavailability of the drug to be approximately 0.65%.[26]

The effect of timing of doses on the systemic absorption of risedronate has been evaluated in a study in 127 healthy volunteers, each of whom was randomised to 1 of 4 groups receiving risedronate 30mg film-coated tablets.[27] Volunteers in group

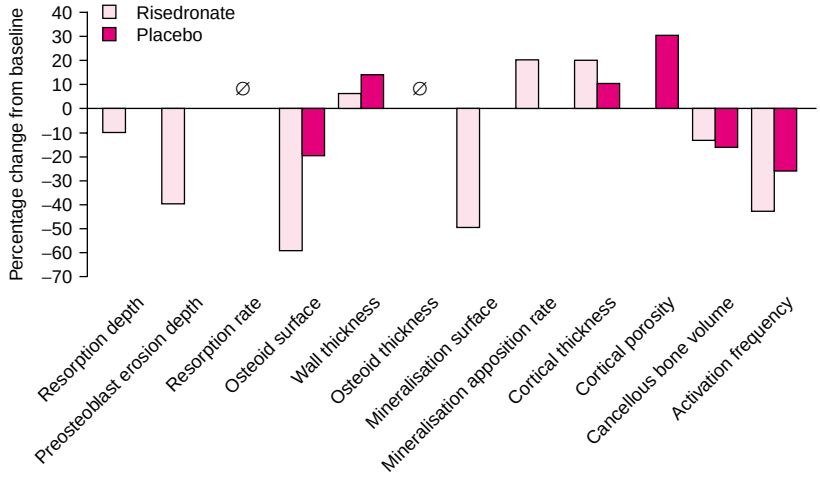

Fig. 2. Effects of risedronate on bone histomorphometry. Changes after 12 months in indices of bone resorption, formation, structure and turnover relative to placebo in iliac crest biopsy tissue from 38 patients who received risedronate 5 mg/day for corticosteroid-induced osteoporosis in a double-blind study (data reported in an abstract; no statistical analysis available).[23] Ø indicates no change from baseline in either group.

1 fasted for 10 hours before and 4 hours after administration, those in groups 2 and 3 fasted for 10 hours and then received risedronate 1 (group 2) or 0.5 (group 3) hours before a high-fat breakfast, and those in group 4 received risedronate 2 hours after a standard dinner.

The extent of absorption of risedronate as shown by mean AUCs from zero to infinity (AUC_∞) was similar for administration 2 hours after dinner (7.35 μg/L · h) or 0.5 hours before breakfast (6.71 μg/L · h). However, absorption was increased approximately 1.5- to 2-fold relative to these values when risedronate was given 1 (AUC_∞ 10.44 μg/L · h) or 4 hours (15.28 μg/L · h) before food. In addition, administration 0.5, 1 or 4 hours before food was associated with rates of absorption (as shown by mean C_{max} values) 2.8, 3.5 and 4.1 times greater, respectively, than that seen with administration 2 hours afterwards.

As with all bisphosphonates, the absorption of risedronate from the GI tract is impaired by the presence of not only food, but also by calcium-(including dairy products), aluminium- and magnesium-containing compounds.[28] Specific directions for administration (section 5) are available to ensure that the systemic absorption of risedronate is maximised in patients who received the drug.

After intravenous administration of risedronate 0.3mg, the volume of distribution (Vd) of the drug at steady state was 6.3 L/kg.[26] Risedronate has a long terminal elimination half-life (480 hours), which probably reflects gradual release of the drug from bone surfaces.[28] Risedronate is excreted unchanged mainly via the kidneys: renal clearance (CL_R) accounted for 87% of total clearance (0.957 L/kg/h) after intravenous administration, which indicates that only a small proportion of systemically available drug is incorporated or 'cleared' into bone.[26] Approximately half of an intravenous dose is excreted in the urine over 24 hours.[29]

Analysis of risedronate excretion in men and women with renal dysfunction [creatinine clearance (CL_{CR}) ranging from 0.9 to 7.6 L/h] has shown CL_R and Vd of the drug to be related in a linear fashion to CL_{CR}.[30] Reductions in predicted CL_R and Vd of 82 and 69%, respectively, were observed when CL_{CR} decreased from 7.2 to 1.2 L/h. These changes were accompanied by a 64% reduction in oral clearance. Regression analysis indicated that dosage adjustments were likely to be unnecessary in patients with mild to moderate renal impairment (defined by these authors as CL_{CR} >1.2 L/h).

Although specific information on drug interactions is not available, risedronate is known not to induce or inhibit hepatic microsomal cytochrome P450 enzymes.[28] This implies that the risk of any interaction between risedronate and the many drugs that are metabolised by this enzyme system is minimal.

3. Therapeutic Use

3.1 Postmenopausal Osteoporosis

Osteoporosis is a systemic skeletal disease characterised by low bone mass and increased susceptibility to fractures in the absence of other identifiable causes of bone loss. The seriousness of this condition is underlined by the observation from a US source that approximately 40% of Caucasian women aged 50 years can expect to sustain an osteoporotic fracture over their remaining lifetime.[31] The primary cause of postmenopausal osteoporosis is believed to be estrogen deficiency; other risk factors include smoking, low dietary calcium intake, excessive alcohol consumption and sedentary lifestyle.[32,33]

Loss of bone mass is not the only determinant of risk in these patients, but it is by far the most important. It is estimated that a 10% loss of bone mass is associated with a 2- to 3-fold increase in the risk of fracture.[34] In addition, it has been shown that almost 20% of patients receiving calcium supplements only who experience vertebral fracture will have another fracture within 1 year.[35] This underlines the need for prompt intervention with therapies that correct imbalances in bone remodelling as rapidly as possible.

The bone loss associated with estrogen deficiency is related to accelerated bone turnover and

the resulting increase in the so-called 'remodelling space' which accounts for the 10% loss in bone mass that is seen over the first 5 years after menopause.[36] Bisphosphonate therapy is used in these patients to decrease bone turnover and to correct the imbalance between osteoclastic resorption and osteoblastic bone formation.

It is not possible on the basis of known clinical variables to predict definitively the likelihood that an individual will experience osteoporosis and fracture. However, measurement of BMD is recommended to provide an indication of fracture risk.[37,38] In general, dual-energy x-ray absorptiometry (DEXA) has been used most commonly in clinical studies as it can be used to measure BMD of the spine, hip or wrist, the most common sites for osteoporotic fractures, and can be carried out in a few minutes with minimal radiation exposure.[37] Other techniques include single-energy and peripheral dual-energy x-ray absorptiometry, radiographic absorptiometry, quantitative computed tomography and ultrasound densitometry.[37]

Vertebral fracture is a common consequence of osteoporosis, and its incidence provides a definitive end-point in clinical studies of agents used to treat this condition.[39] However, BMD (particularly in the lumbar spinal region and in the neck and trochanter of the femur) is a valuable and clinically relevant marker, especially in studies not sufficiently statistically powerful to detect changes in fracture incidence.

BMD is conventionally expressed in terms of T-scores, which indicate the extent of deviation of the patient's bone mass from the ideal peak bone mass in a reference population of individuals aged 30 years.[40] T-scores from 1 standard deviation (SD) above to 1 SD below this level are considered normal; those ranging from –1 to –2.5 SD indicate low bone mass (osteopenia), and patients at this level should be targeted for treatment if they have additional clinical risk factors (e.g. family history or early menopause).[37] T-scores below –2.5 SD indicate osteoporosis and warrant immediate treatment.[37]

3.1.1 Comparisons with Placebo

Two-year phase II data (reviewed by Goa and Balfour[22]) have shown risedronate 5mg given once daily continuously to be more effective than placebo or cyclical risedronate therapy in increasing BMD in postmenopausal women. The rationale behind the inclusion of cyclical regimens in these studies lies in the adverse effects on bone mineralisation that were a concern when the bisphosphonates were first introduced into clinical practice. Early cyclical regimens usually involved etidronate given as part of 3-month cycles with calcium supplementation.[41,42] Accumulating clinical evidence, however, shows impairment of mineralisation to be much less likely with the more recently developed bisphosphonates. In light of this and the results obtained in the phase II study programme, risedronate has been given continuously in all subsequent clinical trials.

Risedronate has been compared with placebo in a series of 6 well designed multicentre phase III clinical studies in postmenopausal women, 4 of which[15-17,43] involved 4873 patients with low bone mass (table I). Two of these 4 trials recruited women with established osteoporosis (2 or more vertebral fractures[15,17] or 1 vertebral fracture and lumbar spine T-score of –2 or less[15]) at baseline; the primary efficacy end-point in these trials was the change in incidence of vertebral fracture over the 3-year period of treatment. The other 2 studies focused on the reversal of loss of bone mass as shown by changes in BMD in women with lumbar spine T-scores of –2 or less at recruitment.[16,43] The vertebral fracture studies[15,17] involved only women who had experienced menopause at least 5 years previously, whereas one of the BMD studies[16] also included women with a more recent history of menopause. The abstract for the other BMD study did not give this information.[43]

A fifth trial[44] assessed the role of risedronate in the prevention of loss of bone mass in 383 generally younger women with recent menopause (within 6 months to 3 years) who had not developed osteopenia or osteoporosis. The final study[45] examined the effect of risedronate on the incidence of

hip fracture in 9331 elderly women, and is discussed in more detail later in this section.

Patients received calcium supplementation in all trials. In all fully published studies,[15-17,45] clear details were given of methods used to account for variation between centres in end-point measurement. These included centralised assessment of x-rays and BMD readings, maximum possible standardisation of DEXA equipment, and calculation of standardised BMD at baseline to adjust for differences in instrumentation.

Effects on Vertebral Fracture Incidence

Statistically significant improvements relative to placebo in vertebral fracture incidence were seen consistently with risedronate 5mg once daily (table I). Because of smaller treatment effects, the lower dosage of 2.5 mg/day was discontinued by protocol amendment in both trials in which vertebral fracture incidence was the primary end-point.[15,17] New vertebral fractures were identified in these studies by the radiographic detection of a decrease of at least 15% in anterior, posterior or middle vertebral height in a vertebra that was normal at baseline. A semiquantitive assessment was also used, in which vertebral condition was graded radiographically on a 4-point scale.

In both vertebral fracture studies,[15,17] significant reductions relative to placebo in vertebral fracture risk were evident with risedronate treatment by the end of the first year (65[15] and 61%;[17] both $p \leq 0.001$) in patients who received risedronate 5 mg/day. The risk of new fractures was reduced over 3 years by 41 ($p = 0.003$ *vs* placebo)[15] and 49% ($p < 0.001$).[17] Vertebral fracture incidence was also reported in one of the BMD studies.[16] This trial lacked the power to detect between-group differences in incidence of vertebral fracture, but a strong trend towards a lower incidence of fracture (defined as a decrease in any vertebral height ratio of more than 3 SD from the mean value for the study population) with risedronate 5 mg/day than with 2.5 mg/day or placebo was noted after 24 months. Analysis of pooled data from 3 clinical trials[15,16,43] has shown a 70% reduction relative to placebo in risk of first vertebral fracture in women with no pre-existing fractures and low BMD of the lumbar spine (T-score ≤–2.5) who received risedronate.[46] Further subset analysis has indicated a significant reduction relative to placebo after 1 year's treatment with risedronate of vertebral fracture risk in women with 2 or more fractures at baseline.[47]

There were also substantial 3-year reductions in the risk of nonvertebral fracture (39[15] and 33%[17]), with statistical significance ($p = 0.02$ *vs* placebo) being attained in 1 (the larger) of the vertebral fracture studies (1641 patients at enrolment in the risedronate 5 mg/day and placebo groups).[15] This was not a primary end-point, however, and it was noted that the smaller vertebral fracture trial (816 patients at enrolment in the risedronate 5 mg/day and placebo groups)[17] lacked the statistical power to detect a treatment difference with respect to nonvertebral fracture.

Effects on Bone Mineral Density

Statistically significant improvements relative to placebo in spine and hip BMD with risedronate 5 mg/day were noted from 6 months onwards in the vertebral fracture studies.[15,17] After 3 years, mean treatment differences of 5.9, 6.4, 3.1 and 2.1% were reported for the lumbar spine, femoral trochanter, femoral neck and midshaft radius, respectively (all $p < 0.001$ *vs* placebo), in 1 trial[17] (table I). Increases in midshaft radius BMD in this and 1 other study[43] are of interest because they reinforce femoral neck data that show beneficial effects of risedronate on predominantly cortical bone sites (the lumbar spine consists chiefly of trabecular bone).

In the 2 studies in which change in mean lumbar spine BMD in patients with low bone mass at baseline was used as the primary end-point,[16,43] risedronate 5 mg/day was consistently more effective than placebo (both with calcium supplementation) [table I]. Mean lumbar spine BMD increased by 4.1% from baseline over 2 years in 1 study ($p < 0.001$ *vs* placebo),[16] and by 4.7% over 18 months ($p < 0.05$ *vs* placebo) in the other[43] (table I).

Mean BMD was increased significantly relative to baseline and placebo at the lumbar spine and

Table I. Randomised, double-blind placebo (PL)-controlled phase III studies of risedronate (RIS) in the prevention and treatment of postmenopausal osteoporosis. Effects on bone mineral density (BMD) and incidence of vertebral fracture

Reference	No. of pts enrolled (mean age in years)	Regimens	Duration	Cumulative % of pts with new vertebral fractures (no. of pts with evaluable x-rays)	BMD (statistically significant mean % changes from baseline)		
					lumbar spine	femoral neck	femoral trochanter
Ebeling et al.[44] (abstract)[a]	383 (52.7)	RIS 2.5 mg/day + Ca 1 g/day	2y	NR	↔	↔	↑1.39
		RIS 5 mg/day + Ca 1 g/day		NR	↑1.98*	↑0.78*	↑2.46*
		PL + Ca 1 g/day		NR	↓2.48	↓2.46	↓1.88
Fogelman et al.[16][b]	184 (65)	RIS 2.5 mg/day + $CaCo_3$ 1 g/day	2y	13 (60)	↑1.4	↔	↑1.7
	177 (65)	RIS 5 mg/day + $CaCO_3$ 1 g/day		7 (40)	↑4.1***	↑1.3***	↑2.7***
	180 (64)	PL + $CaCo_3$ 1 g/day		14 (125)	↔	↔	↔
Harris et al.[15][c]	817 (69)	RIS 2.5 mg/day + Ca[d]	1y[e]	Year 0-1: 3.8* (618)	NR	NR	NR
	821 (69)	RIS 5 mg/day + Ca[d]	3y	Year 0-1: 2.4** (669) Years 0-3: 11.3** (696)	↑5.4*	↑1.6*	↑3.3*
	820 (68)	PL + Ca[d]	3y	Year 0-1: 6.4 (660) Years 0-3: 16.3 (678)	↑1.1	↓1.2	↓0.7
McClung et al.[43] (abstract)[f]	212 (NR)	RIS 2.5 mg/day + Ca 1 g/day	18mo	NR	↑2.8*[g]	↑1.6*[g]	↑3.2*[g]
	216 (NR)	RIS 5 mg/day + Ca 1 g/day		NR	↑4.7*[g]	↑3.0*[g]	↑4.8*[g]
	220 (NR)	PL + Ca 1 g/day		NR	↔	↔	↑1.4[g]
Reginster et al.[17][c]	410 (71)	RIS 2.5 mg/day + Ca[d]	2y[e]	Year 0-1: 7.1* (329)	↑5.5*[g,h]	↑0.8*[g,h]	NR
	408 (71)	RIS 5 mg/day + Ca[d]	3y	Year 0-1: 5.6*** (333) Years 0-3: 18.1*** (344)	↑7.2***[g]	↑2.1***[g]	↑*** (value NR)
	408 (71)	PL + Ca[d]	3y	Year 0-1: 13 (334) Years 0-3: 29 (346)	↑1.3	↔	↓ (value NR)

a Prevention study.

b Patients with history of menopause ≤5 years or >5 years included.

c Patients with history of menopause ≥5 years included only.

d Ca supplementation equivalent to 1 g/day of elemental Ca given. Cholecalciferol (up to 500 IU/day) was given to pts with low serum levels (<40 nmol/L) of 25-hydroxycholecalciferol at baseline.

e RIS 2.5 mg/day arm discontinued early by protocol amendment because of greater improvement with no excess incidence of adverse effects in pts receiving RIS 5 mg/day.

f Time since menopause not stated.

g Estimated from graph.

h Two-year data.

Ca = calcium; **$CaCO_3$** = calcium carbonate; **NR** = not reported; **pts** = patients; ↑ indicates a statistically significant increase from baseline; ↓ indicates a statistically significant decrease from baseline; ↔ indicates no statistically significant change; ***** $p \leq 0.05$, ****** $p < 0.01$, ******* $p \leq 0.001$ *vs* PL.

femoral trochanter by risedronate 2.5 or 5 mg/day by 6 months in the study for which full details are available.[16] After 2 years' treatment with risedronate 5 mg/day, mean lumbar spine BMD increased by 4.2% from baseline in women with a history of menopause of 5 years or less; an increase of 4% was reported in women who had experienced menopause more than 5 years previously.[16] Corresponding decreases in patients receiving placebo were 2.4 and 0.4%. A total of 426 women (62 with recent menopause and 364 with menopause more than 5 years previously) was included in this analysis.

Prevention of Loss of Bone Mass

A preliminary report of the 2-year bone loss prevention study in women with recent menopause (within 6 months to 3 years)[44] showed statistically significant increases relative to both baseline and placebo with risedronate 5 mg/day in spinal and hip BMD from as early as 3 months after starting treatment. After 2 years, BMD had fallen to a statistically significant extent relative to baseline at the lumbar spine and femoral neck and trochanter with placebo, whereas there were statistically significant increases at all sites with risedronate 5 mg/day (table I).

Effect on Hip Fracture Risk in Elderly Women

The efficacy of risedronate treatment in the prevention of hip fracture over 3 years in elderly women has been assessed in a recent large multinational placebo-controlled study.[45] Patients were stratified into 2 groups:

- those aged 70 to 79 years with osteoporosis as shown by femoral neck T-score below –4 or below –3 with at least 1 clinical risk factor for hip fracture (group 1; 3624 patients randomised to risedronate and 1821 to placebo)
- those aged 80 years or over with at least 1 clinical risk factor for hip fracture or low BMD at the femoral neck (T-score below –4 or femoral neck T-score below –3 with a hip axis length of 11.1cm or more) [group 2; 2573 patients randomised to risedronate and 1313 to placebo].

Patients received risedronate at a dosage of 2.5 or 5 mg/day. Calcium supplementation in the form of calcium carbonate at a dosage equivalent to 1g of elemental calcium daily was given to all patients, with supplemental calciferol being given to patients with baseline serum 25-hydroxycholecalciferol levels below 40 nmol/L. The primary end-point was the incidence of radiographically confirmed hip fracture. The mean duration of treatment was 2 years, and was similar for risedronate and placebo recipients.

Overall, risedronate significantly reduced the risk of hip fracture in elderly women with confirmed osteoporosis, but not in those selected for treatment primarily on the basis of nonskeletal risk factors rather than BMD data. In group 1 (patients with confirmed osteoporosis at baseline), hip fracture incidences were 1.9% with risedronate and 3.2% with placebo (relative risk 0.6; $p = 0.009$) [table II]. Most notably, among the 1703 women in group 1 with evidence of at least 1 vertebral fracture at baseline, the relative risk of hip fracture associated with risedronate treatment was 0.4 ($p = 0.003$ *vs* placebo). The corresponding relative risk in 2648 group 1 women known not to have a history of vertebral fracture was 0.6 ($p = 0.14$). There was no significant effect of risedronate treatment on hip fracture risk in group 2 (patients aged 80 years and over, 58% of whom were recruited on the basis of the presence of nonskeletal clinical risk factors only). Hip fracture incidences of 4.2 and 5.1% were reported for the risedronate and placebo groups, respectively ($p = 0.35$) [table II].

Across both groups, incidences of hip fracture were 2.8% in all women who received risedronate, and 3.9% in those who received placebo (relative risk 0.7; $p = 0.02$) [table II], which indicates a significant overall risk reduction with active treatment over the 3 years of the study.

Only 16% of patients in group 2 were recruited on the basis of low BMD at the femoral neck (information on BMD was not available for most of the women in this group). However, in women assigned to placebo treatment ($n = 1313$), the incidence of hip fracture in the 908 patients with unknown BMD was 3.6%, with a corresponding incidence of 5.6% in the 89 women with T-scores

Table II. Effect of risedronate on hip fracture incidence in elderly women. Results of a study in women aged 70 to 79 years with osteoporosis (group 1) and women aged 80 years and over with at least 1 clinical risk factor for hip fracture (group 2).[a] Patients were randomised to treatment with risedronate 2.5 or 5mg[b] or placebo once daily (with calcium supplementation, and cholecalciferol where required) for 3 years[45]

Group		Risedronate		Placebo		Risk of hip fracture (risedronate *vs* placebo)	p (risedronate *vs* placebo)
		no. of patients	incidence of hip fracture (%)	no. of patients	incidence of hip fracture (%)		
1. Women aged 70 to 79 years with confirmed osteoporosis	All patients	3624	1.9	1821	3.2	0.6	0.009
	Vertebral fracture confirmed at baseline	1128	2.3	575	5.7	0.4	0.003
	No vertebral fracture at baseline	1773	1.0	875	1.6	0.6	0.14
2. Women aged 80 years and over with at least 1 clinical risk factor		2573	4.2	1313	5.1	0.8	0.35
Combined results (groups 1 and 2)		6197	2.8	3134	3.9	0.7	0.02

a Group 1: 5445 patients (1821 assigned to placebo and 1812 each to risedronate 2.5mg and 5mg). Group 2: 3886 patients (1313 assigned to placebo, 1281 to risedronate 2.5mg and 1292 to risedronate 5mg) [intention-to-treat population].

b Risedronate dosage groups were combined for comparison with placebo.

above –2.5. The lack of a marked difference between these 2 groups, together with the high incidence of hip fracture in the 316 group 2 placebo patients with confirmed osteoporosis (T-score –2.5 or lower; 9.7%), suggests that the majority of patients in group 2 did not have osteoporosis. Incidences of fracture in the 941 group 2 patients known to have low BMD at baseline were 7.2% in risedronate recipients and 9.7% in women assigned to placebo (p = 0.37 between groups).

3.1.2 Efficacy in Combination with Estrogen

A further study (available as an abstract only) has been carried out in which women with a history of menopause of at least 1 year (mean 14 years) were randomised to double-blind treatment with either risedronate 5 mg/day (n = 261) or placebo (n = 263) in addition to estrogen therapy (0.625 mg/day).[48] All patients received calcium supplementation, and medroxyprogesterone was prescribed for all those with an intact uterus. The mean baseline lumbar spine T-score was –1.3.

As shown in figure 3, increases in BMD with risedronate plus estrogen were equal to or greater than those with estrogen alone at all sites and at all time points. Improvements with risedronate plus estrogen were significantly ($p < 0.05$) greater than those with estrogen alone at 6 months for the lumbar spine and at 12 months for the femoral neck and midshaft radius.

3.2 Glucocorticoid-Induced Osteoporosis

Although many groups of drugs are associated with bone demineralisation and osteoporosis, glucocorticoids merit particular attention in this respect because of their widespread use in a range of inflammatory conditions and in immunosuppression, and because of the significance of their effects on bone turnover (as well as a range of other metabolic functions). The exact prevalence of glucocorticoid-induced osteoporosis is not known, but it is estimated that between 30 and 50% of patients who receive glucocorticoid therapy for more

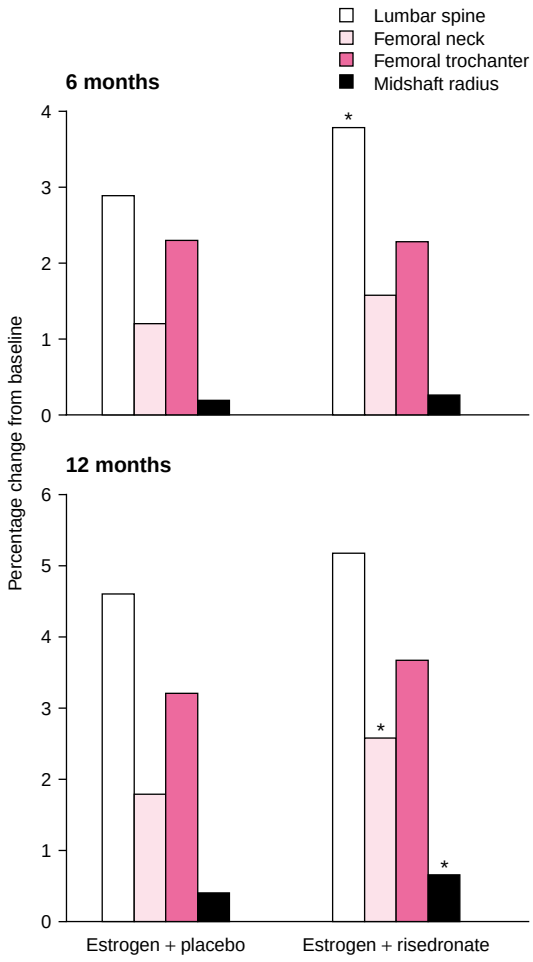

Fig. 3. Effect of risedronate plus estrogen on bone mineral density (BMD) in postmenopausal women. Patients with a mean T-score of –1.3 at baseline were randomised to double-blind treatment with risedronate 5 mg/day (n = 261) or placebo (n = 263) plus estrogen 0.625 mg/day. Calcium supplementation was given to all patients, with calciferol where required. Results are shown for 6 and 12 months at sites where BMD was measured. All increases except midshaft radius at 6 months were statistically significant relative to baseline (data reported in an abstract).[48] * $p < 0.05$ *vs* estrogen + placebo.

than 6 months experience osteoporosis-related fractures.[49] Glucocorticoids affect mainly trabecular bone, and the extent of bone demineralisation is dependent on the dosage given and the duration of therapy.[50] According to results from 244 235 oral corticosteroid users and 244 235 control patients in the UK General Practice Research Database, fracture risk increases with increasing dosages of prednisolone.[51]

Glucocorticoid-induced osteoporosis was originally recognised by Cushing and described in 1932 as part of the syndrome that bears his name.[52] It became apparent soon after the introduction of synthetic glucocorticoids into clinical practice some years later that patients receiving prolonged therapy tend to develop vertebral fractures.[53] Most of the bone loss is usually seen during the first 6 to 12 months of treatment, and evidence suggests that dosages of prednisone above 7.5 mg/day (or equivalent dosages of other glucocorticoids) cause clinically significant trabecular bone loss in most patients.[54-59]

The physiological mechanisms behind glucocorticoid-induced osteoporosis are not fully understood, but decreased osteoblast activity and life span appear to be involved. Increased bone resorption, reduced intestinal calcium absorption and reduced renal tubular reabsorption of calcium may also contribute (reviewed by Eggelmeijer[60] and Hamdy[50]). Glucocorticoid-induced bone loss can be reduced by lifestyle modification, selection of minimum effective glucocorticoid dosages and optimum routes of administration (e.g. topical rather than systemic if possible), and by ensuring that patients receive adequate daily amounts of calcium and calciferol.[50] Drug treatments are also available to inhibit bone resorption or to enhance bone formation: agents that reduce bone loss may be introduced at the beginning of glucocorticoid therapy (primary prevention) or after development of low BMD (with or without fractures) [secondary prevention and treatment].[61]

Risedronate maintained or increased BMD in 2 randomised double-blind placebo-controlled multicentre phase III clinical studies in patients receiving glucocorticoids. One trial[62] focused on the prevention of osteoporosis in men and women starting glucocorticoid treatment, and the other[63] studied patients already on long term glucocorticoid therapy who had low BMD (with vertebral frac-

tures in approximately one-third of patients) at baseline. In both studies, patients (the majority of whom were receiving glucocorticoid therapy for rheumatic conditions) were randomised to treatment with risedronate 2.5 or 5mg once daily or placebo with calcium supplementation for 12 months. Calciferol was also given to all patients in the treatment study.[63]

Patients were stratified according to gender and menopausal status, and those who had received drugs known to affect bone metabolism or who had had hyperparathyroidism, hyperthyroidism or osteomalacia during the preceding year were excluded. BMD was measured by DEXA according to predetermined procedures and on specified equipment. The primary end-point was lumbar spine BMD; secondary end-points included femoral neck and trochanter and distal and midshaft radius BMD. Vertebral fracture incidence was also determined (by spinal radiography), although the studies lacked the statistical power to detect differences between treatments with respect to this parameter.

Of the 228 patients enrolled in the prevention study,[62] 150 completed 12 months' treatment; the mean daily dose of prednisone (or equivalent) over the course of the study was similar between groups and ranged from 10.9 to 11.2mg. Over 12 months, BMD at the lumbar spine, femoral neck and femoral trochanter decreased significantly ($p < 0.05$) from baseline by approximately 3% in placebo recipients (table III). In contrast, BMD was maintained at the lumbar spine and femoral neck, and was increased at the femoral trochanter, in patients receiving risedronate 5 mg/day. Least squares mean differences from placebo were 3.8, 4.1 and 4.6%, respectively (all $p < 0.001$).

BMD was also maintained in patients receiving risedronate 2.5 mg/day, although differences from placebo were less marked and were significant only at the lumbar spine and femoral trochanter (table III). Distal and midshaft radius BMD did not change significantly relative to baseline in any group, and there were no statistically significant differences from placebo with either active treatment.

Table III. Randomised, double-blind placebo (PL)-controlled phase III studies of risedronate (RIS) in the prevention[62] or treatment[63] of glucocorticoid-induced osteoporosis. Effects over 12 months on bone mineral density (BMD) and incidence of vertebral fracture

Reference	No. of pts enrolled [mean age (y)]	Regimens	Cumulative % of pts with new vertebral fractures (no. of pts with evaluable x-rays)	BMD (statistically significant mean % changes from baseline)		
				lumbar spine	femoral neck	femoral trochanter
Cohen et al.[62]	75 (59.5)	RIS 2.5 mg/day + $CaCO_3$ 500 mg/day	11.1 (27)	↔**	↔	↔**
	76 (61.9)	RIS 5 mg/day + $CaCO_3$ 500 mg/day	5.7 (53)	↔***	↔***	↑1.4***
	77 (57.2)	PL + $CaCO_3$ 500 mg/day	17.3 (52)	↓2.8	↓3.1	↓3.1
Reid et al.[63]	94 (59)	RIS 2.5 mg/day + Ca 1 g/day + calciferol 400 IU/day	5 (60)	↑1.9	↔	↔
	100 (58)	RIS 5 mg/day + Ca 1 g/day + calciferol 400 IU/day	5 (60)	↑2.9***	↑1.8**	↑2.4**
	96 (59)	PL + Ca 1 g/day + calciferol 400 IU/day	15 (60)	↔	↔	↔

Ca = calcium; **$CaCO_3$** = calcium carbonate; **pts** = patients; ↑ indicates a statistically significant increase from baseline; ↓ indicates a statistically significant decrease from baseline; ↔ indicates no statistically significant change; * $p < 0.05$, ** $p \leq 0.01$, *** $p < 0.001$ *vs* PL[62] or between groups (3-way analysis of variance).[63]

Subgroup analysis showed statistically significant responses to treatment with risedronate 5 mg/day in men and postmenopausal women, but not in premenopausal women. Possible reasons for this observation may have been the small number of women in the premenopausal subgroup (20% of the total study population) or the protective effect of circulating endogenous estrogen.

In the 12-month study in 290 patients with low bone mass at baseline (mean lumbar spine T-score –1.63), risedronate 5 mg/day significantly increased BMD relative to placebo at the lumbar spine and the femoral neck and trochanter (table III).[63] Across the 2 studies, there was a consistent trend towards a reduction in incidence of vertebral fracture with risedronate 5 mg/day. Analysis of combined data has indicated a 70% reduction in incidence of vertebral fracture relative to placebo ($p = 0.01$) with this dosage of risedronate,[64] although it should be noted that the individual studies were not designed with adequate statistical power to measure this end-point.

Analysis of pooled data from both studies showed that risedronate 5 mg/day increased BMD or prevented bone loss relative to placebo at both the spine and the hip in men.[65] A trend towards lower overall incidence of vertebral fracture with risedronate 5 mg/day than with placebo (9.1 *vs* 23.7%; $p = 0.12$) was also noted. As this analysis involved a limited number of patients (186 men in total), and the studies were not designed to measure gender-specific differences between treatments, these findings require confirmation.

3.3 Paget's Disease

Paget's disease of bone is predominantly a disease of middle or old age, and is characterised by marked localised acceleration of osteoclastic activity followed by proliferation of osteoblasts.[66-68] The osteoblasts, however, do not restore skeletal structure correctly, and lay down a mixture of abnormal lamellar and primitive woven bone. Haphazard mineralisation leads to the formation of thickened and deformed bones of poor structural quality.[66,67] Radiographic examination reveals localised rarefraction of bone, which is manifested by advancing lytic wedges in long bones and *osteoporosis circumscripta* in the cranium. Patients present with combinations of musculoskeletal, neurological and other symptoms, of which pain is the most common.[67]

The efficacy of risedronate in the management of Paget's disease has been investigated in 4 clinical studies,[18-21] one of which[21] was a randomised double-blind comparison with etidronate. In all trials, serum levels of ALP were used as an indirect marker of the effect of treatment on bone turnover and served as the primary end-point. Direct measurements of bone turnover (such as scintigraphy or quantitative histomorphometry) were not used, but the effect of treatment on levels of pain was assessed in 3 trials.[18,19,21]

3.3.1 Noncomparative and Dosage-Finding Studies

In nonblind studies,[18-20] patients had moderate to severe Paget's disease as shown by serum ALP levels at baseline of at least 3 times the upper limit of the normal range in use at each institution, together with relevant clinical history and radiographic and/or scintigraphic findings. Two of the trials shared a similar design in that patients received risedronate 30mg once daily for 84 days with follow-up for a further 112 days.[18,19] Treatment was repeated in patients whose serum ALP levels did not normalise or who experienced disease relapse (defined as an increase of at least 25% from the serum ALP nadir) during the first cycle. Of 20 and 160 patients evaluated in the first[18] and second[19] studies, respectively, 19 and 90 received 2 courses of treatment. The number of patients evaluated for pain at baseline in the second study was 162.

Mean serum ALP levels were statistically significantly reduced from the first post-baseline measurement at day 29 onwards ($p < 0.0001$[18] or 0.001[19] *vs* baseline). The same levels of statistical significance were obtained for reductions in urinary levels of hydroxyproline (expressed as a ratio relative to urinary levels of creatinine) in both studies (table IV). ALP normalisation rates were 65[18]

and 53.8%[19] across 2 treatment cycles. Pagetic pain was reported at enrolment by 70% of patients in both studies. In the first, smaller study,[18] this proportion had fallen to 25% after treatment cycle 1, and all patients were free from pain by day 56 of the second cycle. In the second considerably larger study,[19] 37% of 159 patients had no pain on day 84, and 42% of 154 were free from pain on day 196 ($p < 0.001$ *vs* baseline).

Although conclusions that may be drawn from these studies are limited by the lack of a control group in either, and by the very small number of patients recruited in one,[18] overall findings were nevertheless consistent. It should also be noted that the reference ALP range quoted in the first study[18] was at a level approximately twice that normally expected;[69,70] no explanation was offered by the authors for this.

The third nonblind study was carried out to compare 3 dosages of risedronate [10 (n = 20), 20 (n = 21) and 30mg (n = 21) once daily], each given for 28 days, with follow-up for a total of 85 days.[20] By day 85, mean serum ALP levels were reduced relative to baseline by 48, 57.9 and 72.2%, and normalisation of serum ALP levels was reported in 5, 9.5 and 14.3% of patients, in the risedronate 10, 20 and 30 mg/day groups, respectively ($p = 0.012$ for treatment effect by repeated measures analysis). Transient decreases in serum levels of calcium and increases in serum levels of intact parathyroid hormone in all 3 studies were consistent with the observed reductions in bone turnover. In addition, histological examination of iliac bone formed during risedronate therapy showed the formation of normal lamellar bone rather than the woven bone characteristic of Paget's disease (see also section 4).[20]

3.3.2 Comparison with Etidronate

Risedronate has been compared with etidronate in a randomised double-blind multicentre study in 123 patients.[21] Inclusion criteria included radiographic or scintigraphic evidence of Paget's disease with serum ALP level at least twice the upper limit of the normal range (specified as 31 to 110 IU/L for patients aged ≤58 years and 35 to 115 IU/L for those aged over 58 years). Exclusion criteria were as expected for this type of study and included a history of hyperparathyroidism, hyperthyroidism or osteomalacia during the year preceding recruitment, and the previous use of drugs likely to affect bone turnover (these included most notably calcitonin or calciferol/calcitriol at therapeutic dosages during the month preceding enrolment, and bisphosphonates, fluoride or parathy-

Table IV. Response to risedronate treatment of markers of bone turnover in Paget's disease. Changes relative to baseline in serum alkaline phosphatase (ALP) and urinary hydroxyproline (HDP) levels in 2 noncomparative studies in which patients with serum ALP levels ≥3 times the upper limit of normal received risedronate 30 mg/day for 84 days, with follow-up for a further 112 days. Patients whose serum ALP levels did not return to normal or who experienced relapse[a] received a second cycle of treatment. All changes were statistically significant relative to baseline ($p < 0.001$[19] or 0.0001[18])

Reference	Patients			Mean reduction from baseline in serum ALP level at day 196 (%)		Mean reduction from baseline in urinary HDP : creatinine ratio at day 196 (%)		Proportion of patients responding[b] (%)
	no. evaluated	mean age (y)	mean serum ALP level at baseline (IU/L)[c]	cycle 1	cycle 2[d]	cycle 1	cycle 2[d]	
Hosking et al.[18]	20	74	1696	79.5	86.3	85.5	101.3	100
Siris et al.[19]	160	68.4[e]	800.7	65.7	69.1	50.4	66.9	90

a Defined as an increase of ≥25% from the ALP nadir during treatment.

b Defined as a decrease of ≥50% relative to baseline in serum ALP level during treatment. Figures shown are totals for both treatment cycles.

c Normal laboratory ranges were quoted as 80 to 280 IU/L[18] or 35 to 115 IU/L.[19]

d 19[18] and 90[19] patients received 2 cycles of treatment.

e Mean value for total enrolled cohort of 162 patients with pain evaluation at baseline.

roid hormone during the preceding 6 months). Patients were randomised to treatment with risedronate 30mg once daily for 2 months (n = 62) or etidronate 400mg daily for 6 months (n = 61), with use of placebos to maintain blinding. All patients were followed for an additional 6-month treatment-free period, with optional extended follow-up to a total of 18 months.

Effects on Biochemical Markers

Both risedronate and etidronate were associated with statistically significant ($p < 0.01$) reductions from baseline in serum levels of ALP from the first (1-month) assessment onwards. Overall, the response to risedronate therapy was greater than that seen with etidronate, however ($p < 0.001$ between treatments). Maximum mean changes from baseline were seen after 6 months and were 69% for risedronate and 33% for etidronate (serum ALP responses over 12 months are shown by category in figure 4). Biochemical remission (i.e. normalisation of serum ALP levels) was achieved in 77 and 11% of evaluable risedronate and etidronate recipients, respectively, at month 6 ($p < 0.001$). Relapse (defined as an increase of at least 50% from the serum ALP nadir to at least twice the upper limit of the normal range) was reported over 12 months in 3% of risedronate and 15% of etidronate recipients ($p < 0.05$). After 18 months, 17 (53%) of 32 evaluable patients in the risedronate group and 4 (14%) of 29 evaluable etidronate recipients had serum ALP levels within the normal range.

A past history of etidronate treatment had no effect on the response to risedronate therapy but was associated, as might be expected, with attenuated responses to etidronate. Serum bone-specific ALP levels and urinary deoxypyridinoline : creatinine ratios were also measured in this study, and showed response patterns consistent with those for total serum ALP [normalisation of serum bone-specific ALP levels in 73 and 18% ($p < 0.001$), and of urinary deoxypyridinoline : creatinine levels in 87 and 57% ($p < 0.01$), of risedronate and etidronate recipients, respectively].

Effects on Quality of Life

Short Form Health Survey results showed no significant changes from baseline in physical functioning and role, general health, vitality, social functioning, emotional role or mental health with either treatment in this study. Risedronate was, however, associated with a significant ($p < 0.01$) improvement relative to baseline in mean pain score, whereas etidronate recipients showed a nonsignificant trend only in this respect. There was nevertheless no statistically significant difference between treatments.

4. Tolerability

4.1 General Profile

Adverse reaction data from clinical studies indicate that risedronate is well tolerated by patients at dosages recommended for clinical use (up to 30 mg/day). Tolerability results from 10 068 individuals included in an assessment of 15 066 patients enrolled in placebo-controlled clinical studies of up to 3 years' duration have shown similar frequen-

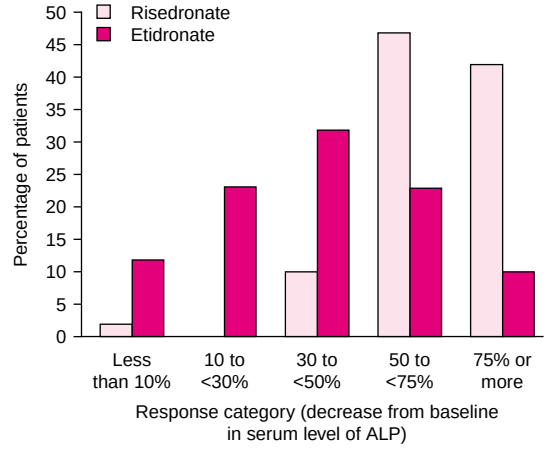

Fig. 4. Effects of risedronate and etidronate on serum alkaline phosphatase (ALP) levels in patients with Paget's disease. Patients were randomised to double-blind treatment with risedronate 30 mg/day for 2 months (n = 62) or etidronate 400 mg/day for 6 months (n = 61). Responses were categorised according to magnitude of reduction from baseline in serum ALP levels, and are shown at 12-month follow-up.[21]

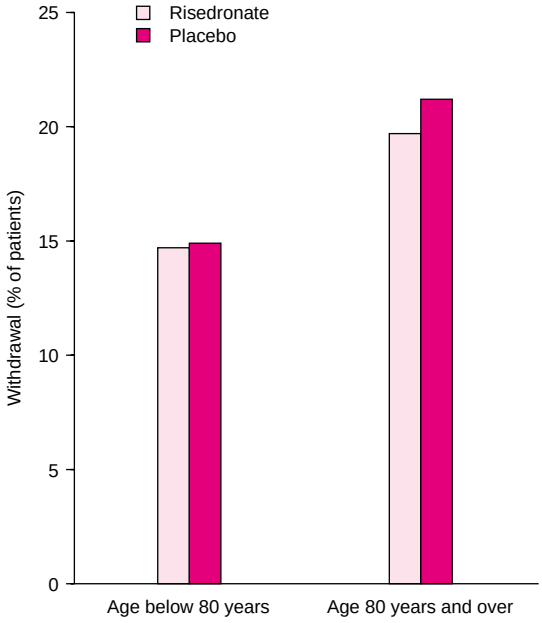

Fig. 5. Rates of withdrawal due to adverse events in patients receiving risedronate 5mg daily. Results from an analysis of tolerability data from placebo-controlled clinical studies of up to 3 years' duration.[71] Data are arranged to show results in patients aged under 80 years (n = 7239) and in those aged 80 years and over (n = 2829).

cies of adverse events with risedronate 5mg daily or placebo.[71] Adverse events were reported by 92.1 and 92.8% of risedronate and placebo recipients, respectively, who were below 80 years of age. Corresponding rates in 2829 patients aged 80 years and over were 87.9 and 88.3%. Withdrawal rates were also similar between treatment groups for both age categories (fig. 5).

Much of the information on the tolerability profile of the drug has been collated from phase III studies of up to 3 years' duration in over 5700 patients with postmenopausal or glucocorticoid-induced osteoporosis in which the tolerability of risedronate 5mg daily was similar to that of placebo.[28,72] Overall incidences of adverse events classified as serious were 24.9% with placebo and 26.3% with risedronate 5 mg/day; respective rates of withdrawal from treatment because of adverse events were 14.4 and 13.5%.[28] Events most commonly reported in patients receiving 5mg/day as tablets are summarised in table V and include infection, back pain, GI symptoms and arthralgia.

Tolerability data are also available from 392 patients with Paget's disease who received risedronate 10 to 30 mg/day for 28 to 84 days in clinical studies.[28,73] In general, as in patients with osteoporosis, adverse events were mild to moderate in nature, did not require discontinuation of treatment and were not related to patient age, gender or race. Risedronate treatment was not associated with any clinically significant changes in laboratory parameters other than those related to bone metabolism.[73]

In the randomised and double-blind comparison of risedronate 30 mg/day for 2 months (n = 62) or etidronate 400 mg/day for 6 months (n = 61) [discussed in section 3.3.2],[21] adverse events with a possible link to study medication were reported in 47% of patients in each treatment group. Six and 8% of patients in the risedronate and etidronate groups, respectively, withdrew from treatment because of adverse events. Comparison of the pooled risedronate data (n = 392) with tolerability results from the 61 patients receiving etidronate in this study showed the most commonly reported adverse events possibly or probably related to study medication in at least 1 patient to be arthralgia (32.8% of risedronate *vs* 29.5% of etidronate recipients), diarrhoea (19.7 *vs* 14.8%), headache (18 *vs*

Table V. Tolerability of risedronate. Incidence of most commonly reported adverse events with a dosage of 5 mg/day in placebo-controlled phase III studies in patients with osteoporosis.[28] Events are shown without attribution of causality, and are from a listing of those seen in more risedronate than placebo recipients

Adverse event	Incidence (%)	
	risedronate (n = 1916)	placebo (n = 1914)
Infection	29.9	29.7
Back pain	26.1	23.6
Arthralgia	23.7	21.1
Pain	13.6	13.1
Abdominal pain	11.6	9.4
Nausea	10.9	10.7
Diarrhoea	10.6	9.6
Hypertension	10.0	9.0

16.4%), abdominal pain (11.5 *vs* 8.2%) and skin rash (11.5 *vs* 8.2%).[28] An influenza-like syndrome was reported in more risedronate than etidronate recipients (9.8 *vs* 1.6%), although the reasons for this are not clear.

Histomorphometric examination of tetracycline-labelled iliac crest biopsies from pagetic and normal bone from 14 patients receiving risedronate 10, 20 or 30 mg/day showed the formation of normal lamellar bone with no evidence of osteomalacia.[73] Furthermore, analysis of 62 pairs of biopsy samples from 31 placebo and 31 risedronate (5mg daily) recipients in one of the vertebral fracture studies reviewed in section 3.1.1[15] revealed no mineralisation problems or marrow abnormalities with risedronate treatment. Indeed, there have been no reports of mineralisation defects in patients receiving risedronate in any clinical trial.

Aminobisphophonates such as pamidronate and alendronate have been associated with an acute-phase reaction (fever, myalgia, mild leucopenia and elevated serum levels of zinc and C-reactive protein) in some patients.[74-76] There was, however, no evidence of such a reaction in 67 healthy individuals who received single oral doses of risedronate 2.5, 5 or 30mg,[77] or in a further 18 volunteers who received single or multiple intravenous doses of 0.1, 0.25 or 0.5mg.[78] In addition, this adverse event has not been reported in clinical trials in patients receiving risedronate.

4.2 Gastrointestinal Events

GI adverse events are a particular concern with orally administered bisphosphonates. Recent data from 15 066 patients who were randomised in clinical studies to receive risedronate 2.5 or 5 mg/day or placebo for up to 3 years have shown no excess incidence of upper GI adverse events with risedronate.[79,80] Patients were not excluded on the basis of underlying GI disorders or NSAID/aspirin use. Incidences of upper GI adverse events were similar for risedronate 5 mg/day and placebo in 3900 patients with a history of upper GI disease (29.5 *vs* 29%), 6336 patients using NSAIDs or aspirin (both 25%), and 2043 patients using histamine H_2-receptor antagonists or proton pump inhibitors (51.5 *vs* 50%).

Of the above patients, 497 underwent endoscopy for GI symptoms. There was no excess of confirmed upper GI lesions in patients receiving risedronate.[79,80]

In a recent study in which healthy postmenopausal women were randomised to single-blind treatment with risedronate 5 mg/day or alendronate 10 mg/day for 2 weeks, overall rates of gastric ulceration (after endoscopic examination on days 8 and 15) were 4.1 and 13.2% in 221 and 227 evaluable risedronate and alendronate recipients, respectively ($p < 0.001$).[81] Mean oesophageal and duodenal erosion scores were similar between treatments, but the mean gastric erosion score with risedronate (39.4% overall for day 8 or day 15) was significantly lower than that with alendronate (60.8%; $p < 0.001$ between groups). Oesophageal ulcers were noted in 3 alendronate and no risedronate recipients, whereas duodenal ulcers were present in 1 and 2 individuals, respectively. Risedronate 5 mg/day has also shown upper GI tolerability similar to that with placebo in a study in 66 women who were unable to tolerate alendronate 10 mg/day.[82]

Higher dosages of risedronate (30 mg/day) and alendronate (40 mg/day) have been compared with placebo or placebo plus aspirin in a 28-day randomised and double-blind study in 235 men and postmenopausal women with normal upper GI endoscopy at baseline, 231 of whom completed the study.[83] Mean gastric erosion scores after endoscopy on day 29 were similar for risedronate (0.73; n = 87) and alendronate (0.89; n = 89); both scores were substantially lower than that seen with aspirin (3.07; n = 20). The mean placebo score was 0.31 (n = 36). Gastric ulcers and/or large numbers of gastric erosions were seen in approximately 3% of risedronate and alendronate recipients, and in 60% of patients who received aspirin.

Analysis of pooled placebo-controlled clinical trial data (see section 4.1)[71] from patients aged 80 years or over with osteoporosis showed similar incidences of upper GI symptoms (18.9 and 20.3%) with risedronate 5 mg/day (n = 1422) or placebo (n

= 1407), respectively. As stated earlier, patients were not excluded because of a history of GI disorders or NSAID/aspirin use. Comparison with patients aged less than 80 years showed no evidence of any age-related increase in adverse event reporting: upper GI adverse events were reported by 24.4% of 3598 risedronate recipients and 23.5% of patients randomised to placebo.[71]

5. Dosage and Administration

Risedronate is presented for clinical use as 5 and 30mg film-coated tablets for oral administration. In order to minimise the risk of upper GI irritation and to maximise the absorption of the drug, it is recommended that tablets be taken once daily at least 30 minutes before the first meal or drink (other than water) of the day.[28,84,85] Dosage directions for some countries also suggest that risedronate may be taken at other times of the day [as long as food or drink (except water) is not consumed for 2 hours either side of each dose] or at least 30 minutes before bedtime.[86,87]

Risedronate tablets should be swallowed by patients in an upright position and with a full glass of water, and patients should not lie down for at least 30 minutes after taking the medication. Tablets should not be sucked or chewed.[28,84,85]

Supplemental calcium and calciferol should be given if dietary intake is found to be inadequate, although calcium (together with some other medicines) may impair GI absorption of risedronate (see section 2) and should therefore be taken at a different time of day.[28]

For the treatment or prevention of postmenopausal or glucocorticoid-induced osteoporosis, the recommended dosage of risedronate is 5mg daily. Patients with Paget's disease should received 30mg daily for an initial treatment period of 2 months. Additional treatment (same dosage and duration) may be considered after at least 2 months' post-treatment observation if serum levels of ALP fail to normalise or disease relapse is seen.[28,84,85]

Although studies in rats indicate the transfer of small amounts of risedronate in maternal milk, it is not known whether the drug is excreted in this manner by humans. Data pertaining to the use of risedronate in pregnant women are also lacking. The manufacturer does not recommend the use of risedronate in patients with severe renal impairment (CL_{CR} <1.8 L/h), although no dosage adjustment is necessary in elderly patients or those with CL_{CR} 1.8 L/h or above.[28]

6. Place of Risedronate in the Management of Resorptive Bone Disease

Risedronate is the latest of the bisphosphonates, a group of drugs that represents a major advance in the nonhormonal management of resorptive bone disease, to be developed. The basic carbon-phosphate structure of this series of compounds lends itself to chemical manipulation to a degree that has enabled researchers to produce a series of active agents with improved antiresorptive potency, tolerability profiles and pharmacokinetic characteristics relative to the first compound, etidronate. A further aim of bisphosphonate research is to minimise or eliminate the risk of mineralisation defects that proved to be a problem in some patients after the introduction of etidronate into clinical practice.[9]

The majority of clinical studies of risedronate have been carried out in patients with osteoporosis, with particular emphasis on the postmenopausal form of this disorder. A good selection of well designed trials of up to 3 years' duration is available to show the efficacy relative to placebo of risedronate 5 mg/day in the treatment of women with established postmenopausal osteoporosis, with early and sustained significant clinical improvement as measured by fracture incidence and BMD being reported consistently. Data from a single trial of 2 years' duration are also available to show prevention of bone loss by this dosage of the drug in women with recent menopause who had not developed osteopenia or osteoporosis at the time of randomisation (see section 3.1.1).

Analysis of subsets of data from the clinical study programme in women with postmenopausal

osteoporosis has indicated that vertebral fracture incidence increases with the number of fractures already experienced, and that subsequent fractures occur early (within 1 year).[35] These findings imply that rapid reductions in fracture risk and prevention of first fracture are of key importance in the management of osteoporosis. Thus, the demonstration of efficacy after 1 year of risedronate treatment in terms of the preferred clinical end-point of vertebral fracture incidence in 2 major studies,[15,17] and pooled subset data showing reduced risk of first vertebral fracture with risedronate in women with low BMD (section 3.1.1),[46] are particularly noteworthy.

Efficacy of risedronate was shown consistently across clinical trials in terms of the commonly used surrogate end-point of BMD, which was assessed in all studies and has been reported to be a useful and responsive outcome measure.[88] In addition, recently reported data from a large placebo-controlled trial have shown risedronate to reduce significantly the risk of hip fracture in elderly women with confirmed osteoporosis (section 3.1.1). This finding is of particular interest in light of the high levels of disability and rates of death associated with hip fracture in this patient group.[89]

The importance of effective treatments for postmenopausal osteoporosis is underlined by the statistics attached to this disease, some of which were discussed earlier in this review (section 3.1). While there has been much discussion of this topic in the literature and speculation that the development of the bisphosphonates might signal the potential eradication of postmenopausal osteoporosis as a clinical problem,[90] it should be noted that a number of therapeutic options are available for the management of this disorder. Hormone replacement therapy (HRT) is an established approach to the management of osteoporosis, and has been shown to reduce bone loss substantially and thereby the risk of osteoporotic fractures.[91,92] HRT also ameliorates menopausal symptoms and protects against ischaemic heart disease, and may also offer protection against dementia; however, it is also associated with withdrawal bleeding, adverse effects such as migraine, and increased risk of thromboembolic disease and breast cancer (reviewed by Barman Balfour and Goa[93]).

Other therapeutic options include calcitonin and the selective estrogen receptor modulators (SERMs). Calcitonin has analgesic properties, but has only moderate effects on BMD. The SERM raloxifene reduces fracture risk, together with beneficial effects on circulating levels of low density liprotein cholesterol, but can cause hot flushes and increase the risk of thromboembolism (reviewed by Barman Balfour and Goa[93]). Lifestyle changes, such as increased levels of appropriate exercise and avoidance of tobacco and excess alcohol, and provision for adequate daily intake of calcium and calciferol should also feature in treatment plans and clinical trial design.

HRT has been recommended for first-line use,[91,92] particularly in younger women with established osteoporosis, while bisphosphonates have been stated to be of particular use in older women who are unable or unwilling to receive HRT (chiefly because of the adverse hormonal effects associated with this type of treatment).[92] The results of the hip fracture study discussed in section 3.1.1[45] are of particular interest in this respect, as they show clearly the efficacy of risedronate in elderly women with osteoporosis. The statistically significant benefit relative to HRT alone in terms of BMD that was seen when risedronate was added to HRT (section 3.1.2) is interesting in light of previous comment in the literature that there is no evidence that the combination of HRT with a bisphosphonate is more effective than either treatment given alone.[91] Most recent consensus guidelines focus on new developments in this rapidly evolving field, and highlight a range of treatments and the importance of individual assessment,[38] although reports of randomised controlled studies comparing risedronate with other treatments are currently not available.

Although fewer data are available than for postmenopausal osteoporosis, the efficacy of risedronate 5 mg/day relative to placebo in the prevention and treatment of glucocorticoid-induced

osteoporosis has been demonstrated in 12-month phase III studies (section 3.2). Maintenance or improvement of bone mass was shown in terms of BMD, with consistent trends towards reduced vertebral fracture incidence with active treatment. Combined analysis[64] has shown a reduction relative to placebo in risk of vertebral fracture at the lumbar spine of 70% with risedronate 5 mg/day. Subgroup analyses indicate that risedronate treatment is effective in patients treated with corticosteroids for up to 3 months or more than 6 months, in both men and women, and in the presence of a variety of underlying conditions.[64] Studies with sufficient statistical power to detect significant differences between treatments in fracture incidence are now required to confirm these findings.

As with the postmenopausal form of the disorder, a number of therapeutic interventions are available for the management of glucocorticoid-induced osteoporosis. These have been comprehensively summarised and reviewed as part of the preparation of UK consensus management guidelines.[94] The majority of clinical trials of bisphosphonate therapy have involved cyclical regimens of etidronate, although clodronate and pamidronate have also been studied. Other interventions include HRT (which is recommended if hypogonadism is confirmed) for both pre- and postmenopausal women, and testosterone therapy for men. Bisphosphonate therapy is the treatment option of choice in patients with normal hormonal function or in those who are unable or unwilling to receive hormonal therapy.[94] Calcitriol may also be considered, although regular monitoring of serum calcium levels is required, and fluoride or intranasal calcitonin are also available as potential alternatives. Risedronate has not yet been compared with any of these agents in patients with glucocorticoid-induced osteoporosis.

There is a need for economic evaluation of all interventions used to treat osteoporosis, including risedronate and other bisphosphonates. To date, most available material focuses on the postmenopausal use of HRT, and no pharmacoeconomic studies of the treatment of glucocorticoid-induced osteoporosis have been published.[95] Further data are required to show the likely economic benefit to healthcare providers and society of the treatment options available, and to illustrate more clearly their effects on quality of life and well-being of patients. Such studies would also assist clinicians in the choice of the most appropriate intervention(s) for each individual patient.

Risedronate is effective at a dosage of 30 mg/day in the reduction of bone turnover and the promotion of the formation of normal lamellar bone in patients with Paget's disease (section 3.3). The majority of available studies were carried out in a nonblind fashion and involved small numbers of patients, but nevertheless showed consistent evidence of clinical improvement in terms of changes in biochemical markers of bone turnover (section 3.3.1). Most notably, risedronate 30 mg/day for 2 months was significantly more effective in terms of markers of bone turnover and pain scores than etidronate at the recommended dosage of 400 mg/day for 6 months in a well designed study in patients with Paget's disease (section 3.3.2).

The biochemical markers of bone turnover used in this study (serum levels of total and bone-specific ALP and urinary levels of deoxypyridinoline) are noted as reliable clinical indicators.[96] Bone pain also responds to the action of anti-osteoclastic drugs, and decreased pain levels accompany clinical improvement and normalisation of bone remodelling (although a placebo effect may be present in up to 30 to 40% of patients).[96] Although available data indicate a beneficial effect of risedronate on bone pain in patients with Paget's disease (sections 3.3.1 and 3.3.2), the presence of placebo controls in future studies would show more clearly the true magnitude of the effect of the drug in this respect.

The bisphosphonates are now considered to be first-line therapy in Paget's disease, and risedronate should be viewed in this light. Early experience with the drug is promising, and future comparisons with other bisphosphonates will clarify its overall position. Further clinical experience and more extensive studies are needed to demonstrate long

term improvements in bone strength and patient wellbeing and reduction of Pagetic complications in individuals treated with risedronate.

Risedronate has been shown to have a good tolerability profile in clinical trials (section 4). Frequencies of adverse events have been generally similar to those with placebo, with no evidence of acute-phase reactions or mineralisation defects. There have been no concerns over GI tolerability in studies carried out to date.

In conclusion, risedronate is an effective and well tolerated novel bisphosphonate that is suitable for first-line therapy in Paget's disease. The rapid and sustained reductions in vertebral fracture incidence and BMD changes seen in patients with postmenopausal and glucocorticoid-induced osteoporosis indicate the drug to be a valuable treatment option with first-line potential, particularly in patients for whom hormonal therapy is inappropriate. The effects of the drug on hip fracture incidence in elderly women with confirmed osteoporosis point to a particular role in older patients, or those with more advanced disease.

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