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EXPERT REVIEW

Risedronate Sodium for the Treatment of Osteoporosis and Paget's Disease: The Evidence of its Therapeutic Value

Phoebe E. Stanford[1,2] and Jacqueline R. Center[1–3]

[1]Osteoporosis and Bone Biology, Garvan Institute of Medical Research, [2]Department of Endocrinology, St. Vincent's Hospital Clinical School, [3]School of Medicine, University of New South Wales, 384 Victoria St., Darlinghurst, NSW, Australia.
Corresponding author email: j.center@garvan.org.au

Abstract: Risedronate is a third generation bisphosphonate used in the prevention of osteoporotic fractures and the treatment of Paget's disease. In patients with osteoporosis, risedronate reduces bone turnover, improves bone density and reduces the risk of both vertebral and non-vertebral fractures. Efficacy has been established in the treatment of postmenopausal osteoporosis, osteoporosis in men, and in osteoporosis secondary to glucocorticoids. There is a rapid onset of effect with a reduction in bone turnover seen within 1 month and fracture risk reduction as early as 6 months. In Paget's disease treatment with risedronate reduces bone turnover and improves bone pain. Short term treatment results in a sustained benefit.

Keywords: risedronate, bisphosphonates, osteoporosis, fracture, Paget's disease

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Introduction

Risedronate is a third generation bisphosphonate with proven efficacy in prevention of osteoporotic fractures,[1,2] and in Paget's disease.[3–5] This review will focus on the evidence for the use of risedronate in the treatment of osteoporosis and Paget's disease.

Osteoporosis is a systemic skeletal disease characterised by reduced bone mass and altered architecture resulting in a predisposition to fractures. Osteoporotic fractures result in increased morbidity reduced quality of life, and premature mortality.[6] In addition they are associated with a significant social and economic burden. The treatment aim in osteoporosis is to prevent fractures, and a decrease in fracture rate is a required endpoint for regulatory approval for osteoporosis treatment. Currently, several approved treatment options exist for the management of osteoporosis that effectively reduce the risk of vertebral, non-vertebral, and hip fractures.[7] There are two broad groups of treatment, antiresorptive agents, which slow bone resorption and anabolic agents which stimulate bone formation. Of the antiresorptive drugs, bisphosphonates, constitute the largest class, and can be used across a broad spectrum of causes of osteoporosis, including postmenopausal, male, and steroid-induced osteoporosis.

Paget's disease of bone is a focal bone disorder characterized by excessive osteoclastic bone resorption followed by osteoblastic bone formation. It is associated with morphological and functional abnormalities of osteoclasts. The result is the production of architecturally abnormal and mechanically weaker bone. The abnormal bone remodelling disrupts normal bone architecture and structure, leading to the development of various complications including bone pain, deformity, pathological fracture and secondary osteoarthritis.[8] The goal of treatment in Paget's disease is to normalise bone turnover, with the aim of achieving sustained remission.[9] The traditional treatment for Paget's disease has been short-term therapy with bisphosphonates.

Mechanism of Action

Bisphosphonates are related to pyrophosphate, a naturally-occurring substance with a high affinity for calcium crystals. In bisphosphonates, the oxygen atom that binds the two phosphorus atoms in pyrophosphate (P–O–P) is substituted by a carbon (P–C–P) which renders them resistant to degradation.[10] Bisphosphonates have two additional side-chains in their molecule that are not present in pyrophosphate, termed R1 and R2, that are attached to the central, germinal carbon atom. Differences in these side chains account for the differences between the various bisphosphonates, with small changes in structure leading to differences in bone affinity.[11] (Fig. 1)[10]

Bisphosphonates are taken up by the skeleton, primarily at active remodelling sites. They are preferentially taken up by osteoclasts due to their ability to release the bound drug from bone in the acidic environment of the resorption lacunae. Older bisphosphonates without a nitrogen atom in their molecule (etidronate, clodronate) are incorporated into ATP and generate metabolites which induce osteoclast apoptosis.[10] The newer nitrogen-containing bisphosphonates (ibandronate, pamidronate, alendronate, risedronate, zolendronate) cause changes in the cytoskeleton of osteoclasts, such as loss of ruffled border, disruption of actin rings and altered vesicular trafficking, leading to their inactivation and potentially apoptosis.[12] This is primarily due to interfering with farnesyl pyrophosphate synthase (FPPS), an enzyme responsible for the formation of isoprenoid metabolites required for the prenylation of small GTPases that are important for the function and survival of osteoclasts.

Due to differences in the structure of the R1 and R2 group each bisphosphonate has a unique profile of biochemical potency on FPPS and potential differences in mineral affinity. The rank order of each of these properties is as follows.[11]

- Mineral affinity: clodronate < etidronate < risedronate < ibandronate < alendronate < pamidronate < zoledronate.
- FPPS enzyme inhibition: etidronate = clodronate (extremely weak inhibitors) <<<< pamidronate < alendronate < ibandronate < risedronate < zoledronate.

Thus risedronate has high FPPS enzyme binding and moderate bone affinity compared with other bisphosphonates. The potential significance of these differences is explained below under "Pharmacokinetics and Metabolism" and in the section "Place in Therapy".

Risedronate decreases the rate of bone turnover, and maintains trabecular and cortical microarchitecture.[13]

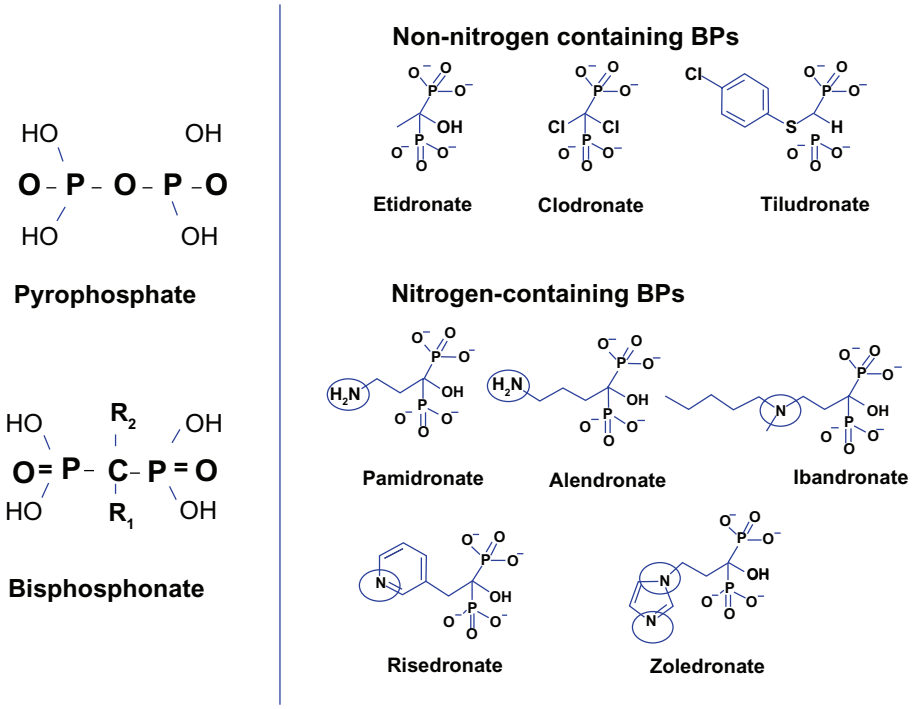

Figure 1. Structures phrophosphate and bisphosphonates.
Note: The acid forms are depicted.

The first effect is a decrease in the rate of bone resorption, due to its effect on osteoclasts, which is followed by a slower decrease in the rate of bone formation due to the coupling of the two processes. This results in establishment of a new steady state that is reached at a lower rate of bone turnover. In the first months of treatment, before a new steady state between bone resorption and formation, there is dissociation between the two processes leading to a transient positive bone balance. With continuing treatment, bone remodelling space is decreased, leading to a further increase in bone density.[10] The decrease in bone turnover with risedronate is associated with fracture risk reduction.[14] In Paget's disease the effect of risedronate on bone turnover leads to normalisation of alkaline phosphatase and reduced pain for prolonged periods of time in the majority of patients.[15]

Pharmacokinetics and Metabolism

Risedronate is rapidly absorbed throughout the upper gastrointestinal tract, however its mean bioavailability is only 0.63% which is substantially decreased by up to 90% when administered with food.[16] Food and drink contain polyvalent cations including calcium that form complexes with the bisphosphonates resulting in them being unable to be absorbed. Even a dose given between meals and at least 2 hours from a meal results in the bisphosphonate being less effective than when given in the complete fasting state.[17]

By nature of the stable P–C–P group at its backbone, risedronate is resistant to chemical and enzymatic hydrolysis, and as a result there is no systemic metabolism. Approximately half of the absorbed drug is excreted in the urine within 24 hours. The amount taken up by the skeleton depends on renal function and prevalent rate of bone turnover. Unabsorbed drug is eliminated unchanged in the faeces.

Elimination is multiphasic, with an initial half life of 1.5 hours, and an exponential half life of 480 hours, which is hypothesised to represent the dissociation of risedronate from bone surfaces (although the elimination rate from human bone is unknown).[16] Following resumption of bone remodelling at previously exposed sites, risedronate that has been embedded in bone will be released from the hydroxyapatite crystals. It is not known to what extent the released drug may be active locally again, however, this pharmacokinetic property is probably responsible for the slow reversal of the effect on bone resorption observed in clinical studies. Differences in bone-binding affinity among

bisphosphonates may, in theory, affect the rate of reversal of the effect on bone resorption. For example, following cessation of risedronate, bone turnover markers (eg, urinary N-telopeptide (NTX)) have been shown to return to control group levels after one year,[18] in contrast to alendronate, where urinary NTX remained suppressed in the first year off treatment.[19] This would be consistent with Risedronate's lower mineral binding affinity compared with Alendronate.

Risedronate was initially investigated as a 5 mg daily dose, and further studies have shown that risedronate 35 mg once weekly,[20] and 150 mg once a month have equivalent efficacy. These studies were of one year duration, and the endpoint was improvement in bone density. There was no significant difference in the percentage of patients with new vertebral fractures between treatments, although the number or new vertebral fracture was small.

More recently a delayed release preparation of risedronate with an enteric coating (Actonel EC) has been developed which ensures adequate bioavailability and pharmacological availability of risedronate without the requirement to take risedronate prior to the first food or drink in the morning. The 35 mg once-a week enteric-coated tablet delivers risedronate beyond the stomach where concentrations of substances that interfere with its absorption are lower. The formulation also includes a chelating agent which binds cations such as calcium that may be present in the area of absorption. A recent study has shown that this formulation is as effective as the standard 5 mg daily dose.[21] This study randomised 923 postmenopausal women (mean age 66) to either daily 5 mg risedronate taken at least 30 minutes before breakfast or 35 mg enteric-coated risedronate taken either at least 30 minutes before breakfast or immediately after breakfast. Patients were eligible if they had a lumbar spine or total hip BMD corresponding to a T-score of –2.5 or lower or a T-score of –2.0 or lower with at least one prevalent vertebral fracture. This study was designed to test the non-inferiority (based on the percent change in lumbar spine BMD from baseline after 1 year) of the enteric-coated risedronate 35 mg weekly formulation taken before or after breakfast compared to the 5 mg daily standard risedronate taken per label. The study showed that the enteric-coated risedronate, taken either before or after breakfast was as effective as the standard 5 mg daily preparation in terms of improvement in bone density.

Clinical Studies

This section will describe the evidence for use of risedronate in osteoporosis and Paget's disease; a comparison of risedronate with other available treatments will follow, under 'Place in therapy'.

Osteoporosis

Postmenopausal osteoporosis

The multinational Vertebral Efficacy with Risedronate Therapy (VERT- MN)[1] and the North American Vertebral Efficacy with Risedronate Therapy (VERT- NA)[2] were the pivotal studies forming the basis for the Therapeutic Goods Administration (TGA) approval for the use of risedronate in osteoporosis. These two randomized, studies compared the effect of 5 mg risedronate daily with placebo over 3 years. All subjects received calcium 1000 mg/d and subjects with low baseline levels of 25- hydroxyvitamin D received cholecalciferol (up to 500 IU/d). The studies included over 3000 (n = 2548 VERT- NA and 1226 VERT- MN) postmenopausal women up to age 85 years, with at least two radiographically confirmed vertebral fractures, or in the case of the North American study, one vertebral fracture and lumbar spine T score ≤ -2.0. Average age of the subjects was 71 in the multinational and 69 in the North American study. Mean lumbar spine T-scores were –2.8 in the multinational and –2.4 in the North American study. The primary efficacy measure was vertebral fracture incidence. Other efficacy measures included radiographically confirmed nonvertebral osteoporosis-related fractures, and effects on bone turnover and bone mineral density (BMD).

Fracture reduction

In the VERT- MN the risk of new vertebral fracture was reduced by 49% by risedronate versus control at 3 years, with an incidence of 18% in the risedronate group and 29% in the control group ($P < 0.001$). A similar reduction of 41% was seen in the North American study. Nonvertebral fractures were also reduced by 39% in the North American study over 3 years, as compared with control (5.2% vs. 8.4%; $P = 0.02$). Nonvertebral fractures were also fewer in the VERT- MN, risk reduced by 33% (10.9% vs. 16%), although this study was not powered to detect this.

The above studies were not powered to assess the effect on hip fracture, however risedronate has subsequently been shown to be effective in reducing the risk of hip fractures in a study of elderly women randomised to either risedronate (2.5 mg or 5 mg daily) or placebo.[22] This study enrolled over 9000 women in two groups; one group consisted of women aged 70 to 79 years who had a femoral neck T-score lower than –4.0 or a femoral-neck T-score lower than –3.0 plus at least one clinical risk factor for hip fracture. The other group consisted of women 80 years of age or older who were eligible if they had at least one clinical risk factor for hip fracture, a femoral neck T-score lower than –4.0, or a femoral-neck T-score lower than –3.0 plus a hip-axis length of 11.1 cm or greater, however the majority of the women in this group were recruited solely on the basis of clinical risk factors and information on bone mineral density was not available in the majority. In the group aged 70 to 79 years there was a 40% relative risk reduction (1.9% versus 3.2%; $P = 0.009$) in hip fractures. However, in the group of women 80 years of age or older, risedronate had no effect on the incidence of hip fracture. Therefore this study suggests that risedronate treatment reduces the risk of hip fracture among women with osteoporosis, defined as a low bone mineral density at the femoral neck, but it is not more effective than calcium and vitamin D alone in women identified primarily on the basis of clinical risk factors for hip fracture.

The antifracture effect of risedronate has a rapid onset. Studies, including the aforementioned pivotal trials have shown that risedronate treatment decreases the incidence of clinical vertebral fractures and nonvertebral fractures within 6 months.[1,2,23] A sustained therapeutic effect on fracture risk reduction has been observed after 5 and 7 years of treatment. In a 2 year extension of the VERT- MN study, fracture risk reduction with risedronate was shown to continue, with a 59% risk reduction for new vertebral fractures during the 2 year extension ($P = 0.01$).[24] Of the 220 women who completed the 5 year extension study, 136 women completed a further 2 year extension in which all women received risedronate (5 mg daily). There was no significant difference in the incidence of new vertebral fractures during the 6–7 year period as compared to the risedronate treated patients during years 4–5, suggesting that the anti-fracture efficacy of risedronate is not lost after 7 years of treatment.[25]

In additional studies, risedronate has also been shown to be effective in the prevention of the first vertebral fracture in patients with low BMD and no prevalent vertebral fractures. Heaney et al reported an analysis of data from four placebo controlled randomised studies which included postmenopausal women with osteoporosis (mean baseline lumbar spine T-score –3.27), but without prevalent vertebral fractures. In the overall analysis risedronate resulted in a reduction in the risk of first vertebral fracture by 75%, which was similar both in younger women with a mean age of 64 years and in older women with a mean age of 76 years.[26]

Bone turnover

In both the VERT- MN and VERT- NA there was a significant reduction in bone turnover seen at 1 month, with a nadir reached at 6 months, and bone turnover remained suppressed throughout the study. In these studies there was a reduction in deoxypyridinoline:creatinine ration (Dpd/Cr) and Bone Specific Alkaline-Phosphatase (BAP) in the order of 30%–40%. (Dpd/Cr –33%, BAP –37% in VERT- MN and BAP –35%, Dpd/Cr –38% in VERT- NA (median percentage change from baseline)). Additionally a reduction in NTX/Creatinine ratio in the order of 60% has been demonstated in other studies.[20,25]

Bone density

In both the VERT- MN and VERT- NA there was increased bone mineral density at the lumbar spine and femoral neck and trochanter seen as early as 6 months. In the VERT- NA study bone mineral density increased by 5.4% at the lumbar spine, 1.6% at the femoral neck, and 3.3% at the femoral trochanter over 3 years ($P < 0.05$), while the placebo group showed small but significant changes from baseline over the same period (1.1% at the lumbar spine, –1.2% at the femoral neck and –0.7% at the femoral trochanter). At the midshaft of the radius, the 5-mg risedronate group experienced no significant change (0.2%), compared with a significant ($P < 0.05$) loss in the placebo group of 1.4%. In the VERT- MN study at 3 years bone mineral density increased by 5.9% (95% CI: 4.5–7.3) at the lumbar spine,

3.1% (95% CI: 1.8–4.5) at the femoral neck, 4% (95% CI: 4.9–7.8) at the femoral trochanter, and 2.1% (95% CI: 1.1–1.2) at the midshaft radius, compared to placebo ($P < 0.001$).

Treatment cessation

The effects of discontinuing therapy on clinical outcomes have been studied in both short (2 yr) and long term (7 yr) studies.[18,27] Irrespective of whether treatment was short-term or long-term, following discontinuation of risedronate there was a decrease in bone density and a return of bone turnover markers to control levels within 1 year. However, despite the apparent resolution of effect on bone density and bone turnover, incident vertebral fractures remained significantly lower in the group previously treated with risedronate in the year after discontinuation of treatment (46% lower than the control group, $P = 0.009$).[18]

Osteoporosis in men

Studies have shown risedronate to be an effective treatment of osteoporosis in men.[28,29] In a 2-year, double-blind, randomized, placebo-controlled trial, risedronate 35 mg weekly produced significantly greater reductions in bone turnover markers and increases in bone density at the lumbar spine and proximal femur compared with placebo. The inclusion criteria for this study were a lumbar spine T-score ≤ -2.5 and femoral neck T-score ≤ -1 or lumbar spine T-score ≤ -1 and femoral neck T-score ≤ -2.0. There was no difference in the response between the subgroups of patients with lumbar spine BMD ≤ -2.5 or > 2.5 at baseline. The incidence of new fractures was low and there was no significant difference between the groups. This is likely because men at a higher risk for fractures were excluded, including men who had more than one osteoporosis-related fracture at screening or had one osteoporosis-related fracture within 6 months before screening.[28]

However, fracture risk reduction has been demonstrated with risedronate in men in another randomised study of 316 men with osteoporosis, with or without prevalent vertebral fractures at baseline.[29] In this study inclusion criteria included a baseline lumbar spine T-score of ≤ -2.5 SD and a baseline femoral neck T-score of ≤ -2.0. The mean lumbar spine and femoral neck BMD were approximately −3.3 and −2.5 respectively. The average age was 56 and approximately 50% had at least one vertebral fracture at baseline. Over 1 year, the incidence of new vertebral fractures in the risedronate group was reduced by 60% versus the control group (5.1% versus 12.7%). The incidence of nonvertebral fractures was also reduced (42% reduction), although this did not reach statistical significance

Glucocorticoid induced osteoporosis

A number of double-blind randomized placebo controlled trials have confirmed benefits of risedronate in the prevention and treatment of glucocorticoid induced osteoporosis in both women and men.[30–34]

Wallach et al reported an analysis of the pooled results of two studies of men and women receiving moderate to high doses of glucocorticoids (equivalent to ≥ 7.5 mg daily) randomised to risedronate versus placebo for 1 year. One of the studies included patients who had received glucocorticoid treatment for less than 3 months, and the other included patients on treatment for greater than 6 months, proposed to represent prevention and treatment, respectively. At baseline, the mean lumbar spine BMD was similar in the risedronate and placebo groups, 44% of the patients had a lumbar spine BMD within 1 SD of the young adult reference mean (T-score > -1), 35% were osteopenic (T-score between −1 and −2.5), and 21% had osteoporosis (T-score < -2.5), as defined by the World Health Organization. Approximately one third had prevalent vertebral fractures at baseline.

In the pooled analysis of the studies, patients receiving risedronate had a 70% reduction in vertebral fracture risk compared with placebo (5% versus 16%, $P = 0.01$). A trend towards a reduction in the incidence of vertebral fractures was also observed in each of the individual studies; 71% ($P = 0.07$) in the prevention study and 70% ($P = 0.12$) in the treatment study. There was no difference in nonvertebral fractures between risedronate and placebo groups.

An increase in BMD compared to placebo was seen by 6 months, and at 12 months there was a 2.9% difference at the lumbar spine, 2.8% at the femoral neck and 2.8% for the femoral trochanter in the pooled analysis. Positive effects of risedronate on BMD were also observed in both the individual treatment and prevention studies. Bone turnover markers were decreased from 1 month, and reached a nadir by 6 months. Median urinary NTx levels decreased

by 62%, while median serum BAP concentrations decreased by 20%. The beneficial effects of risedronate on bone density, and vertebral fracture risk were present regardless of the underlying disease or gender.[33]

Paget's Disease

A number of clinical trials have demonstrated that risedronate is an effective treatment for Paget's disease.[3–5,35,36] In an initial uncontrolled study of risedronate in Paget's disease,162 men and women with moderate to severe Paget's disease (mean ALP approximately 7 times the upper limit of normal), were treated with 30 mg risedronate daily for 84 days, followed by a 112 day follow up period without treatment. This was repeated once in patients who did not have normalisation of ALP, or who relapsed (defined as ≥25% increase in ALP from the nadir value in those who had responded). There was a decrease in ALP by 65.7% after the first cycle, and 90% of patients had a ≥50% reduction in serum ALP following the second course. Of those who responded 94% responded during the first treatment period. Normalisation of ALP occurred in 54% of patients during the course of the study, with only 9% of these patients relapsing by the end of the study. In addition, 26% of the patients with bone pain at baseline were pain free at day 196, and 56% of those with severe bone pain had improved.[35]

Subsequently risedronate was compared with etidronate, the first bisphosphonate in use for Paget's disease, in a randomised double blind study. Risedronate (30 mg/day for 2 months) was more effective than oral etidronate (400 mg/day for 6 months) in normalisation ALP levels. At 12 months the ALP concentration normalised in 73% of patients who received risedronate compared with 15% receiving etidronate ($P < 0.001$). Median time to normalisation was shorter; 91 days in the risedronate group compared with 360 days with etidronate ($P < 0.001$). At 18 months 53% of patients in the risedronate group remained in biochemical remission.[3]

Safety

Upper GI adverse events

In general, clinical trials have shown that risedronate is well tolerated, with safety profiles similar to placebo.[1,2,25] While the major side effect of bisphosphonates is upper gastrointestinal (GI) intolerance, in the pivotal studies of osteoporosis described above, there was no significant increase in the incidence of adverse GI events demonstrated compared with placebo.

In a pooled analysis of nine multicenter, randomized, double-blind, placebo-controlled studies, including over 10,000 men and women, with comprehensive, prospective evaluation of GI tract adverse events, daily treatment with 5 mg of risedronate was not associated with an increased frequency of adverse GI effects. Upper GI tract adverse events were reported by 29.6% of patients in the placebo group compared with 29.8% in the risedronate group ($P = 0.77$). Most upper GI tract adverse events were mild and did not require discontinuation from the study. Patients at higher risk, including those taking aspirin, or NSAIDs were not excluded from these studies. Among the 63.0% of higher risk patients using these medications during the study there was no increase in the percentages of patients who reported upper GI tract adverse events in the risedronate group.[37]

Furthermore, there was no increase in the frequency of upper GI adverse events in an analysis of the safety outcomes of two, 2-year, randomised studies of knee osteoarthritis, in which patients were treated with dosages of up to 3 times the daily dose prescribed for the treatment of osteoporosis.[38] In these studies patients were randomly assigned to risedronate once-daily 5 mg, once daily 15 mg, once-weekly 35 mg, once-weekly 50 mg or placebo.

Despite these negative findings of the phase 3 studies, endoscopic studies have demonstrated the development of gastric erosions or ulcers in the first weeks following initiation of risedronate. In two studies where endoscopies were performed at one and two weeks after starting treatment with risedronate 5 mg daily gastric ulcers were observed at rate of 4.1%[39] and 6%,[40] however were there was no placebo comparator in these studies.

Musculoskeletal pain

Bone, joint, and muscle pain has been associated with risedronate, as well as other bisphosphonates. In phase 3 trials joint, neck or bone pain was reported in 17.6% of patients, on risedronate 5 mg daily, compared with 14.6% of the placebo group.[16] The FDA issued a safety warning highlighting the possibility of severe and sometimes incapacitating bone, joint,

and/or musculoskeletal pain that may occur at any point after patients begin taking a bisphosphonate.[41] Stopping treatment may give complete relief of symptoms, though there are cases of slow or incomplete resolution. The pathological basis for the reaction remains unclear.

Osteonecrosis of the jaw

Osteonecrosis of the jaw (ONJ) was defined in 2007 by the American Society for Bone and Mineral Research (ASBMR) task force as an area of exposed bone in the maxillofacial region that did not heal within 8 weeks after identification by a health-care provider in a patient who was receiving or had been exposed to a bisphosphonate and had not had radiation therapy to the craniofacial region.[42] No direct causative relationship has been demonstrated between ONJ and bisphosphonate therapy in patients with osteoporosis.[43] However, some risk factors for ONJ have been identified including trauma to the oral cavity (particularly tooth extraction), the use of immunosuppressive drugs including corticosteroids and poor oral hygiene.

The majority of cases of ONJ have been associated with high doses of intravenous bisphosphonates in the treatment of malignancy. ONJ has been reported with oral bisphosphonates, including risedronate, however the available evidence shows that ONJ is much less common among patients treated with oral bisphosphonates at the doses used for osteoporosis or Paget's disease. While the risk of ONJ in patients with cancer treated with high doses of intravenous bisphosphonates is estimated to be in the range of 1–10 per 100 patients (depending on duration of therapy), the risk of ONJ associated with oral bisphosphonate therapy for osteoporosis, based on review of both published and unpublished data, has been found to be much lower, estimated between 1 in 10,000 and 1 in 100,000 person- years of treatment.[42]

Atypical fractures

The bulk of evidence indicates that the decrease in bone turnover by risedronate, at the doses used in the treatment of postmenopausal osteoporosis, protects skeletal integrity.[13,44] However, there is now evidence from case series implicating bisphosphonates, including risedronate in the development of atypical femoral fragility fractures,[45] although there is no RCT evidence for an increase in the risk of these fractures with any of the bisphosphonates.

One proposed mechanism for this finding is that potent inhibition of bone turnover by bisphosphonates may be harmful by causing increased mineralization, and the accumulation of microdamage leading to brittle bone. The fractures associated with long term bisphosphonates have atypical features and clinical presentation. The fractures are typically subtrochanteric/diaphyseal and patients often describe a period of weeks or months of discomfort at the site before the fracture occurs. The fracture is often reported to occur without trauma such as stepping down a stair, walking, or turning. Radiological features at the fracture site include thickening of the femoral cortex, presence of a transverse fracture, and a cortical beak. A stress reaction or visible fracture line on the contralateral femur is additionally reported in many cases.[46]

Based on available evidence, atypical fractures are rare, with a proposed incidence of 60–100/100,000 patient-years.[46] According to the ASBMR task-force preliminary data from a large US health maintenance organization (HMO) suggested that the incidence may increase with increasing duration of BP exposure, from 2 per 100,000 cases per year for 2 years of BP use to 78 per 100,000 cases per year for 8 years of BP use.[47]

Hypocalcaemia

Although rare, hypocalcaemia has been described with risedronate.[48] This is more likely to occur in patients with very high baseline bone turnover or on those with a condition predisposing to hypocalcaemia such as hypoparathyroidism or vitamin D deficiency.

Efficacy

As discussed above risedronate has proven risk reduction for vertebral and non vertebral fractures in men and women with osteoporosis. In the pivotal trials in postmenopausal women risedronate lead to an increase in bone density, a reduction in bone turnover and reduced the rates of vertebral and non vertebral fractures compared to placebo over 3 years by up to 49% and 39%, respectively.[49] Fracture risk reduction may be seen as early as 6 months,[23] and persists for 1 year after discontinuation despite an increase in bone turnover back to baseline.[18] In men with osteoporosis there are similar results, with a

60% reduction in vertebral fractures compared to placebo after 1 year.[29]

Risedronate is effective in the prevention of glucocorticoid induced bone loss, and reduces the risk of vertebral fracture in both men and women. In addition risedronate has been shown to be effective in the prevention of bone loss in early postmenopausal women (mean age 51 yrs) with normal bone density,[50] however it has not been shown to reduce fractures in this group.

In the treatment of Paget's disease risedronate effectively reduces bone turnover, with 85% of patients having a reduction in ALP of at least 50% and normalisation of ALP in a third of patients after a single 84 day course (30 mg daily).[35] Importantly, the reduction in bone turnover is associated with improvement in bone pain.[36]

Place in therapy

Osteoporosis

There are now a number of available treatment options for the management of osteoporosis, including the bisphosphonates, denosumab, strontium ranelate, raloxifene, tibolone and parathyroid hormone (teriparetide). Among the bisphosphonates with proven efficacy in management of osteoporosis, risedronate, alendronate, and zoledronic acid are now among the most commonly used.

Other bisphosphonates

Alendronate has been compared with risedronate in clinical studies with variable results.[51–54] Randomised controlled trials comparing weekly risedronate 35 mg with weekly alendronate 70 mg have shown that while both treatments result in reduction in bone turnover and an improvement in bone density, there is a significantly greater effect with alendronate at both 1 and 2 years, with similar safety profile.[52,53] Alendronate resulted in a greater reduction in bone resorption markers (NTX 56% versus 43.9% and CTX 73.4% versus 53.1%, $P < 0.001$), and bone formation markers BSAP (40% compared with 29%, $P < 0.001$) and P1NP (62% versus 46% $P < 0.001$) after 24 months. Differences in BMD between treatments was 1.7% at the total hip, 1.9% at the femoral neck, and 1.8% at the lumbar spine after 24 months of therapy ($P < 0.001$).[53] However, in a retrospective observational cohort study using healthcare utilisation data, risedronate was observed to have a 43% lower incidence of hip ($P = 0.01$) and an 18% lower incidence of nonvertebral fractures ($P = 0.03$) than alendronate after 12 months of therapy.[54] Contrary to this a subsequent study using similar methods did not find a significant difference in fracture rates at 1 or 3 years.[51]

Although both alendronate and risedronate appear to have comparable efficacy, there are potential differences. The rate of reversal of the effect may be different with different bisphosphonates, depending on their pharmacological properties, particularly their bone-binding affinity. Compared to alendronate, risedronate appears to have a faster reversal of effect on bone density and bone turnover. Studies of cessation of risedronate have shown a decrease in bone density and a return of bone turnover markers to baseline levels within 1 year.[18,27] By contrast, following alendronate withdrawal bone turnover suppression can remain evident for up to 5 years.[55] While this may be rationalised by risedronate's less strong affinity for hydroxyapatite, there are no head-to-head studies. However, although there was a return of bone turnover to pretreatment levels the incidence of new morphometric vertebral fractures remained lower in the former risedronate group compared with the placebo group 1 year after discontinuation.

Given the potential long turnover suppression, it has been suggested that unlike other chronic diseases which require long term uninterrupted treatment, the treatment of osteoporosis with bisphosphonates may be interrupted, with a so called drug 'holiday'. This concept was based on a study with alendronate (The Fracture Intervention Trial Long-term Extension (FLEX) study) comparing the effects of stopping alendronate treatment after 5 years with continuing for 10 years.[55] This demonstrated that patients who received placebo after 5 years of alendronate therapy had a gradual increase in bone resorption markers; however, they still remained below baseline values. Switching to placebo for 5 years resulted in declines in bone density at the total hip and spine but levels remained at or above pretreatment levels. In addition the risk of nonvertebral fractures was not significantly different between those who continue or stopped treatment. However for vertebral fractures there was an increased risk of clinically recognized vertebral fractures but no significant difference in morphometric vertebral fractures between the

two groups. More recently a study of zoledronate comparing 6 years of treatment followed by 3 years of continued treatment compared with placebo again suggested no difference in nonvertebral fractures, but an increase in new morphometric although not clinical vertebral fractures.[56] Notably there has been no comparable study using risedronate where the more rapid offset may have a more obvious deleterious effect on longer term fracture rates.

The potentially more rapid wearing off of effect with risedronate may be of particular interest in those patients in whom a switch to anabolic therapy with PTH may be contemplated. The use of alendronate in combination with PTH has been shown to impair the ability of PTH increase bone turnover and to increase bone density at the lumbar spine and femoral neck.[57,58] There is some evidence that risedronate has a lesser effect on the response to PTH than alendronate, with an earlier and greater increase in bone turnover in patients previously treated with risedronate.[59]

A once yearly infusion of zoledronic acid has shown to be an effective treatment for osteoporosis in women and men,[60] with reduction in vertebral and non vertebral fractures, as well as a reduction in mortality after hip fracture. The yearly infusion may be preferable for patients in whom problems with absorption or compliance with regular medications may be a concern. The infusion is generally well tolerated, however it is associated with an acute phase reaction characterised by fever, myalgia and arthralgia, usually lasting 24 to 72 hours.

Denosumab

Denosumab, a monoclonal antibody to the receptor activator of nuclear factor-κB ligand (RANKL), is the newest addition to the antiresorptives. In the pivotal FREEDOM study, 60 mg of denosumab injected subcutaneously every 6 months was shown to be effective in reducing vertebral, non-vertebral, and hip fractures in postmenopausal women with osteoporosis. Although there have not been head-to-head studies with bisphosphonates, it appears to be at least as effective as risedronate, with 68% risk reduction in new vertebral fractures, and 20% relative risk reduction in non vertebral fractures over 3 years.[61] Similar to the bisphosphonates, denosumab has been associated with osteonecrosis of the jaw, and although not yet reported, given the potent reduction in bone turnover associated with denosumab it would seem that atypical fractures may be a potential concern with longer term use.

Denosumab should be considered as an alternative first line therapy to bisphosphonates, particularly useful for its lack of gastrointestinal side effects and the potential for use in patients with impaired renal function because it is not cleared by the kidneys. The twice yearly subcutaneous administration could improve long-term adherence, however, the rapid increase of bone turnover markers, starting 6 months after the last injection makes timing of follow up important to maintain its effect.

Strontium ranelate

Strontium Ranelate is another oral antiresorptive treatment option with proven vertebral and non vertebral antifracture efficacy in postmenopausal women.[62,63] Although direct comparative trials have not been performed, the effect appears to be comparable to risedronate. Similar to oral bisphosphonates absorption is limited by food, and strontium requires daily dosing taken at least 2 hours after and before food.

Treatment is well tolerated, with the major side effect being gastrointestinal intolerance, with diarrhoea and nausea being reported in about 7%, which resolves after 3 months of treatment. However in analysis of phase III studies, increased rates of deep venous thromboembolism has been reported with strontium. Unlike the bisphosphonates osteonecrosis of the jaw and atypical fractures have not been reported with strontium. Bone mineral density measurement by dual-energy x-ray absorptiometry is amplified by the strontium content of bones and leads to an overestimation of bone mineral density which may cause problems in the monitoring of osteoporotic patients by DXA scanning.

Selective oestrogen receptor modulator, raloxifene

Raloxifene, a selective oestrogen receptor modulator, has been shown to reduce vertebral fractures and reduce the risk of breast cancer. However raloxifene has been associated with exacerbation of menopausal symptoms, and an increased risk of venous thromboembolism, and has not been shown to reduce non vertebral fractures.[64]

Hormone replacement therapy

Hormone replacement therapy is no longer considered a first-line option for the management of postmenopausal osteoporosis since the results from the Woman's Health Initiative. While observational studies suggest that estrogens continue to prevent fractures after decades of use, and the Women's Health Initiative found that the profile of adverse effects of initiating oestrogen in perimenopausal women was better compared with that in older women (fewer strokes, heart attacks, and menopausal symptoms in women on oestrogen than on placebo), there still appears to be a long-term increased risk of breast cancer.[65]

Tibolone, a synthetic selective tissue estrogenic activity regulator, has metabolites with estrogenic, progestogenic, and androgenic activities which produce differential effects in target organs due to tissue-specific metabolism, enzyme regulation, and receptor activation. Tibolone is approved in many countries for treatment of menopausal symptoms, and for the prevention of osteoporosis. In the LIFT study treatment with tibolone at a dose of 1.25 mg daily, half the dose used for treatment of menopausal symptoms, for 3 years resulted in a 45% reduction in the risk of new vertebral fracture. It was also associated with a reduced risk of non vertebral fracture (26%), invasive breast cancer (68%), and colon cancer (69%) and did not appear to have a negative effect on cardiovascular outcomes or thrombosis. However there was a significant increase in stroke, particularly in those patients older than 70, as well as an increase in vaginal bleeding and breast tenderness.[66] In addition, while the LIFT study showed a reduction in breast cancer, the LIBERATE trial which was investigating the efficacy and safety of tibolone for the treatment of menopausal symptoms in women with a history of breast cancer, was halted prematurely because of a trend toward an excess rate of breast-cancer recurrence in women taking tibolone.[67] Therefore tibolone should not be used in patient with risk factors for stroke, or those who have a history of breast cancer.

Teriparetide

Parathyroid hormone is the first anabolic treatment approved for the management of osteoporosis. Whilst the other available treatments reduce bone resorption PTH is the only agent to increase bone formation. Recombinant human PTH 1–34 (teriparatide) administered once daily subcutaneously results in increases bone density in postmenopausal women[68] and in men with osteoporosis,[69] and reduces the risk of fracture in postmenopausal women with osteoporosis. The safety and tolerability profile of teriparatide in clinical trials is good, and although long-term administration of high doses in rats was associated with the development of osteosarcoma, there is no suggestion of an increased rate of osteosarcoma in humans.

Although there are no head-to-head studies comparing risedronate with teriparatide directly, there appears to be similar efficacy in terms of vertebral fracture risk reduction, and a greater reduction in nonvertebral fractures with teriparetide. However, in contrast to risedronate,[22] there is no data to support reduction in the risk of hip fractures with teriparatide due to smaller numbers. Despite its effectiveness, the cost of treatment and the requirement for daily injections means that its use in clinical practise is limited to those patients with more severe osteoporosis, who have failed other therapies. In addition, treatment with teriparetide is limited to 18 months, after which time antiresorptive treatment is required in order to maintain the increase in bone density.

Paget's disease

Bisphosphonates have been the mainstay of treatment for Paget's disease since the introduction of Etidronate. Although Etidronate was an effective treatment, the management of Paget's disease has been greatly improved with the development of the aminobisphosphonates, including risedronate, pamidronate, alendronate and most recently zoledronic acid. In comparison to etidronate, these newer bisphosphonates result in a more rapid onset and longer lasting remission with a shorter duration of therapy.[3,70]

Both risedronate and alendronate are potent oral treatment options, with similar efficacy and tolerability.[71] However, alendronate requires a longer duration of treatment, (40 mg/day for 6 months) compared with risedronate (30 mg/day for 2–3 months) for comparable effect. Pamidronate, which generally requires multiple slow intravenous infusion, has now been superseded by the more potent zoledronic acid, which results in a sustained remission after a single infusion.[72]

A single 5 mg infusion of zoledronic acid has been compared with a 2 month course of risedronate

(30 mg daily) in a preplanned, pooled analysis of two independent randomized controlled trials.[73] In this study zoledronic acid was associated with significantly greater rates of ALP normalization, and superior effects on quality of life measures. Furthermore follow up data of the responders in these studies has shown that zoledronic acid results in a much more sustained response to therapy.[72] At 2 years 98% of patients who received zoledronic acid had a continued benefit compared with 57% of patients treated with risedronate.

Patient Preference

As described above there are now numerous effective treatments available which can be considered first line in the management of osteoporosis. This allows individualisation of treatment to suit a particular patient's needs and desires.

Risedronate may be preferable due to the convenience of weekly or monthly oral dosing. Whilst the efficacy and side effect profile is similar to alendronate, risedronate is now available in an enteric coated preparation, eliminating the restriction of having to have the medication away from food, which is easier for patients and may potentially improve compliance.

Although the risk of osteonecrosis of the jaw is low with oral bisphosphonates, for those postmenopausal women who are particularly concerned about this risk there are alternatives, including strontium, tibolone, or raloxifene. Tibolone may be particularly useful for those who may benefit from its effects on menopausal symptoms. Denosumab may also be an option for these patients as, although cases of ONJ have been reported with denosumab, as its effect on bone turnover is reversible[74] it may be reasonable to arrange for major dental work to be performed after its effect on bone turnover has ceased 6 months post injection.

For patients in whom gastrointestinal side effects are a problem, or in whom oral absorption may be a concern, a parenteral treatment such as denosumab or zoledronic acid may be preferable.

For the treatment of Paget's disease bisphosphonates are the mainstay of treatment. If considering oral dosing Risedronate may be the treatment of choice due to its shorter treatment course as compared with alendronate. However, zoledronic acid, the newest treatment for Paget's disease, given as a single infusion has been shown to have a more rapid onset and more long lasting response when compared with oral therapies such as risedronate and thus many would consider it the treatment of choice.

Conclusions

Risedronate is a potent oral bisphosphonate which is an effective therapy for the management of osteoporosis and Paget's disease. In osteoporosis there is evidence over a wide range of causes of osteoporosis, including in postmenopausal and glucocorticoid related bone loss, and for the treatment of osteoporosis in men. Treatment is well tolerated, and although there have been recent concerns regarding osteonecrosis of the jaw and the potential for atypical fractures with long term use, these events are rare. Although there are now a number of treatment options for the management of osteoporosis, risedronate remains a first line treatment option.

In the treatment of Paget's disease, although risedronate remains an effective therapy, zoledronic acid has been shown to be superior in terms of the degree of disease suppression, with a more rapid onset of action and sustained effect.

Author Contributions

Wrote the first draft of the manuscript: PES. Contributed to the writing of the manuscript: PES, JRC. Agree with manuscript results and conclusions: JRC, PES. Made critical revisions and approved final version: JRC. All authors reviewed and approved of the final manuscript.

Competing Interests

J Center has had international travel expenses paid for by Merck Sharpe and Dohme and Sanofi Aventis. J Center has received honoraria from Novartis, Eli Lilly, Merck Sharpe and Dohme, Sanofi Aventis and Amgen for general practitioner education. P Stanford has no competing interests.

Disclosures and Ethics

As a requirement of publication author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality

and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest. Provenance: the authors were invited to submit this paper.

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