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REVIEW

Efficacy and safety of risedronate 150 mg once a month in the treatment of postmenopausal osteoporosis

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Abstract: Fragility fractures that occur as a result of osteoporosis are frequently associated with chronic pain and decreased quality of life as well as significant morbidity and mortality. Fracture reduction, however, is often less than optimal due to poor compliance with medications. Studies have demonstrated that risedronate, a heterocyclic nitrogen containing bisphosphonate can reduce vertebral, nonvertebral, and hip fracture incidence in postmenopausal women, in men, and in subsets of older patients at great risk of falls and fragility. The mechanism, efficacy, dosing options, and tolerability of risedronate are reviewed.

Keywords: osteoporosis, fracture

Osteoporosis is defined as a systemic skeletal disorder characterized by weakening of bone mineral and tissue and low bone mass. These changes result in compromised bone strength, an increase in bone fragility, and an increased risk of fracture. Although the disorder most commonly affects postmenopausal women, 20% of people affected in the United States are men.

Fractures are commonly classified into two major types: vertebral and nonvertebral fractures. Nonvertebral fractures involve the upper extremity, lower extremity (including the hip), ribs, and pelvis. In fact, with the exception of fractures of the fingers, toes, skull, and face all fractures after the age of fifty are associated with low bone mineral density (BMD).[1] Vertebral fractures are the most common osteoporotic fracture, occurring in approximately 20% of postmenopausal women. However, vertebral fractures often go undiagnosed clinically, and they are the earliest and most common fragility-related fracture in postmenopausal women. In the IMPACT study, between 29.5%–46.5% of vertebral fractures were undiagnosed.[2] Vertebral fractures, whether recognized clinically or not, carry with them increased morbidity and mortality. These fractures lead to kyphosis, difficulty walking because of change in posture, abdominal pain, and potentially respiratory insufficiency.[3] Lindsay and colleagues demonstrated that approximately 20% of postmenopausal women who have a first vertebral fracture will experience another vertebral fracture within one year.[4] Once one vertebral fracture occurs, other fractures are likely to follow soon after; 25% of patients with a first vertebral fracture will go on to have another fracture anywhere in the skeleton within one year.[5] Hip fractures carry with them great mortality; approximately 20% of patients with hip fracture patients die within one year, and 30%–50% of these patients never regain their original functional status which they had before the hip

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fracture.[6] These statistics will take on even more significance with time. By the year 2050, the incidence of hip fractures in the world is expected to increase by 240% in women and 310% in men.[7]

Excellent treatment is available to reduce the risk of fracture in women and men as well as to decrease osteoporosis-related mortality. The nitrogen-containing bishosphonates have come to be the most widely used drugs in the treatment of osteoporosis. There are three oral bisphosphonates which are US Food and Drug Administration (FDA)-approved: alendronate, risedronate, and ibandronate, and two intravenous bisphosphonates: ibandronate and zolendronate. Other FDA options for treatment of osteoporosis include raloxifene, hormone replacement therapy, calcitonin, and teriparatide.

Management of osteoporosis

Bisphosphonates are highly potent inhibitors of osteoclastic bone resorption, with an initial filling in of resorption cavities, followed by increased mineralization that is a result of the reduced bone turnover.

The three FDA approved oral bisphosphonates: alendronate,[8] risedronate,[9] and ibandronate[10] have all demonstrated significant vertebral fracture risk reduction, respectively. In addition, Black and colleagues demonstrated vertebral fracture reduction with intravenous zolendronate as a once yearly therapy.[11] Furthermore, alendronate,[8] risedronate,[12] and zolendronate[11] have proven significant hip fracture reduction. Risedronate[9,12] and zoledronate[11] also have documented nonvertebral fracture data (Table 1).

Pharmacology

Bisphosphonates are stable chemical P-C-P analogs of inorganic pyrophosphate, which itself is characterized by a P-O-P structure. Stability is conferred by the carbon atom replacing the oxygen atom between the two phosphates. This renders the molecule resistant to degradation. Bisphosphonates have a high binding affinity to hydroxyapatite in bone and are therefore taken up preferentially by the skeleton. When osteoclasts resorb hydroxyapatite bound to bisphosphonate through endocytosis bone resorption is then impaired. There are significant differences among the bisphosphonates in the way they bind to bone mineral, which may in turn explain some differences in potency, speed of onset, and offset action and safety.[13]

Bisphosphonates have two side groups: R1 and R2. Modifications to one or more of these side groups can reduce the affinity of the drug for bone as well as decrease its biochemical potency. R1 substituents such as hydroxyl or amino increase absorption to mineral[14] while changing R2 leads to differences in antiresorptive potency.[15]

Pamidronate and alendronate have free amino groups in their side chains. Ibandronate has a highly substituted nitrogen side chain. Risedronate and zoledronate have nitrogen-containing groups within heterocyclic rings. It is the nitrogen-containing group which inhibits farnesyl pyrophosphate synthase (FPPS) along the mevalonate pathway.[16] FPPS generates isoprenoid lipids that are used for post-translational changes of small GTP-binding proteins needed for regulation osteoclast function.

The order of potency in inhibiting FPP synthase is: zoledronate > risedronate > ibandronate > alendronate.[13] Binding affinities of each individual bisphosphonate also contribute to their antiresorptive potency. Nancollas and colleagues documented that the R2 side chain determines this binding function, with the following binding differences: zolendronate > alendronate > ibandronate > risedronate.[18] Risedronate is, therefore, a highly potent inhibitor of FPPS, but does not bind to mineral as strongly as alendronate or zoledronate. Russell and colleagues proposes that this lower mineral binding may enable risedronate to have a wider distribution within bone.[13] These qualities may explain some of its unique pharmacologic effects on bone such as early vertebral fracture data. Clinical vertebral fractures were not planned endpoints in the early bisphosphonate trials. However, post-hoc analysis of the risedronate trials show a significant effect on vertebral fracture as early as six months (not seen with the other oral antiresorptives), suggesting an earlier onset to action than other bisphosphonates.[17] Two observational studies shed more information about the differences among the bisphosphonates. In the PROTECT study there was an evaluation of women on calcitonin, alendronate, and risedronate. Patients treated with risedronate had a significantly lower incidence of nonvertebral fractures after six and 12 months compared with calcitonin and alendronate.[19] In the REAL study, another observational study, the outcomes of patients on alendronate and risedronate were evaluated. After six and 12 months patients on risedronate had significantly lower numbers of hip fractures compared to patients on alendronate.[20]

Intestinal absorption of bisphosphonates is between 0.6%–3% of an orally administered bisphosphonate.[21] The absorption of all bisphosphonates is decreased in the presence of food, most likely because they form a complex with divalent cations contained in food such as calcium. Therefore, bisphosphonates should be taken on an empty stomach with a plain glass of tap water (ie, not mineral or

Table 1 Summary of fracture data among bisphosphonates

Reduction in radiographically defined fractures in PROSPECTIVE clinical studies	Risedronate (Actonel)	Alendronate (Fosamax)	Ibandronate (Boniva)	Zoledronic acid (Reclast)
Vertebral fractures				
1 Year Vertebral	65% VERT-NA – Harris, JAMA 1999 61% VERT-MN – Reginster, Osteoporosis International 2000	Not Reported – Lieberman, NEJM 1995	Not Measured – BONE – Chesnut, ABMR 2004	60% – HORIZON – Black, NEJM 2007
3 Year Vertebral	41% – VERT-NA- Harris, JAMA 1999	47% – FIT 1 – Black, Lancet 1996	62% -BONE – Chesnut, ABMR 2004	70% – HORIZON – Black, NEJM 2007
4 Year Vertebral	n/a	44% – FIT 2 – Cummings, JAMA 1998	n/a	n/a
Nonvertebral fractures				
3 Year Nonvertebral	39% – VERT NA 20% – HIP NS – 33% – VERT-MN – Reginster – Osteoporosis International 2000	NS – 21% – Lieberman NS – 20% – FIT 1 – Black, Lancet 1996	NS – 10%-BONE – Chesnut, ABMR 2004	25% – HORIZON – Black, NEJM 2007
4 Year Nonvertebral	n/a	NS – 12% – FIT 2 – Cummings, JAMA 1998	n/a	n/a
5 Year Nonvertebral	37% VERT MN extension	n/a	n/a	n/a
Hip fractures				
Hip Fracture Primary Endpoint?	Yes	No	No	Yes
Hip Fractures	60% HIP- McClung, NEJM 2001 – Group 1 – Reduction in patients with confirmed osteoporosis and at least one prevalent fracture at baseline NS – 20% HIP, McClung, NEJM 2001 – Group 2- Patients not selected on basis of low BMD	51% FIT 1 Black, Lancet 1996- Reduction in patients with confirmed osteoporosis and at least one prevalent fracture at baseling *(This data is based on 33 fractures: 22 in the placebo and 11 in the treatment group. If one more patient fractured in the treatment group, this 51% would be NONstatistically significant) NS – 21% FIT 2 Cummings, JAMA 1998 (0.43–1.44) p = 0.44 – patients not selected based on osteoporotic BMD	n/a	41% – HORIZON – Black, NEJM 2007

well water which may contain such cations). Patients taking risedronate are instructed to wait thirty minutes post-dosing before they should eat or drink. They are also instructed not to lie down for at least thirty minutes to avoid esophageal irritation. Approximately 40%–60% of a dose of risedronate is concentrated in the skeleton and the remaining is excreted unchanged in the urine.

Clinical efficacy of risedronate

Oral risedronate has been used in the treatment of postmenopausal osteoporosis for nearly 11 years. It was initially only available as a daily oral dosage regimen of 5 mg per day. In 2002 a weekly regimen of 35 mg became available. In 2007 a twice monthly dosing regimen on two consecutive days was approved by the FDA, and finally, in 2008, a 150 mg monthly dose of risedronate was approved.

Fracture data: Vertebral

Two seminal studies, VERT-North America and VERT-multinational have demonstrated that in patients with post menopausal osteoporosis risedronate increases BMD and reduces vertebral and nonvertebral fractures.[9,22] Inclusion criteria in these studies included at least two or more radiographically confirmed vertebral fractures (T4–L4) or one vertebral fracture and lumbar spine T score of −2.0. In the two studies, risedronate increased BMD by 5.4%–5.9% in the lumbar spine and by 1.6%–3.1% in the femoral neck.[9,22] In both studies daily oral risedronate was associated with a similar vertebral fracture relative risk reduction (0.51 in VERT-NA and 0.59 in VERT-MN). In the larger of the two trials, VERT-NA, risedronate reduced the incidence of vertebral fractures by 65% in just one year, 49% in three years, and reduced nonvertebral fractures by 39% in three years.

Fracture data: Nonvertebral

Nonvertebral fractures account for the majority of health care-related costs in osteoporosis. Wells and colleagues[29] published a review of the clinical efficacy of risedronate in the primary and secondary prevention of osteoporotic fractures in postmenopausal osteoporosis compared with untreated women over a period of at least one year. A total of seven randomized controlled trials were included in the review. Two were prevention trials and five were secondary prevention/treatment trials. Four of the secondary prevention trials could be pooled for analysis and demonstrated a relative risk (RR) of 0.80 (95% confidence interval [CI] = 0.72; p = 0.90) in risk of nonvertebral fractures. Three of the secondary prevention trials were pooled for analysis and demonstrated a RR reduction of 0.74 (95% CI = 0.59; p = 0.94). Only risedronate and zoledronate have been documented to decrease the risk of nonvertebral fractures and hip fractures in an intention to treat population from randomized trials of at least three years duration.[11,12]

Fracture data: Hip

As discussed earlier, hip fractures portend significant morbidity and mortality. Up to 50% of hip fracture patients will have permanent functional disability[30] and hip fracture increases the risk of death by 12%–20%.

The HIP trial was the first randomized controlled trial with a bisphosphonate with hip fracture incidence as the primary outcome. McClung and colleagues[12] demonstrated that risedronate prevented hip fractures in elderly (70–79 years of age) with known osteoporosis by BMD: 1.9% fractures in risedronate group over two years versus 3.2% in placebo (RR 0.6; 95% CI 0.4 to 0.9; p = 0.009). Interestingly, an older group (>80 years) that was chosen primarily on the basis of clinical risk factors for falls and not BMD did not demonstrate any significant reduction in hip fracture. This highlights that bisphosphonates require low BMD to prevent fracture; the drugs cannot prevent falls themselves. Similar findings were seen in the Rotterdam study, in which a large European cohort was followed for risk factors for hip fractures. The study revealed a 10-fold increase in hip fracture between the groups in their late 90's compared to the group in their late 50's despite similar T scores between the two groups. The increase in hip fracture is thought to be caused by factors related to aging and not necessarily to decreases in BMD.[31]

Length of treatment

Safety of bisphosphonates in relation to length of treatment has received much attention at present. However, there are no clear answers. Efficacy with prolonged treatment is well-established. Mellstrom and colleagues[23] documented a continuous increase in lumbar spine and total hip BMD after seven years of treatment. For the first five years of the study, women received 5 mg/day of risedronate or placebo. However, all women who entered a 6–7 year extension study received daily risedronate. A total of 164 women (placebo group, 81: risedronate group, 83) entered the 6–7 years extension study. Incidence of new vertebral fractures during the 6–7 years was similar between the two treatment groups (3.8%). Vertebral fracture incidence did not change in the seven-year risedronate group during the 6–7 years as compared

to the 4–5 years; a significant reduction was observed in the original placebo group that switched to risedronate during the 6–7 years. The incidence of nonvertebral fractures was 7.4% and 6.0% in the placebo/risedronate and risedronate groups in years 6–7, respectively.

Response to drug treatment is obviously well monitored in clinical studies in contrast to the general treatment population. Siris and colleagues[24] collected data from two US claims databases during a five year period, totaling 35,537 women 45 years and older. The women were prescribed either alendronate or risedronate for 24 months. Only 43% were found to be refill compliant and 20% persisted with treatment during the two years. And there was a progressive relationship between refill compliance and fracture risk reduction. Lombas and colleagues found that 50% of all patients don't take oral bisphosphonates regularly.[25]

Dosage options

Because risedronate remains active on bone surface for a relatively long period, an extended dosing interval is possible. In fact, Brown and colleagues demonstrated noninferiority of BMD and markers of bone turnover for the weekly dosage of risedronate compared to the daily dosage.[26] In addition, the incidence of morphometric vertebral fractures was similar between the two treatment groups at both one and two years. Delmas and colleagues demonstrated similar findings with risedronate 75 mg each day for two consecutive days per month.[27]

More recently, once monthly 150 mg risedronate was compared to 5 mg daily in an international phase III, randomized double blind parallel group multicenter study of post menopausal osteoporosis, ie, noninferior.[28] Only results of the first year has been published; the studying is continuing for a second year. The primary endpoint of the monthly study was a noninferiority comparing the least mean percentage change from baseline in lumbar spine BMD in the 150 mg monthly and 5 mg daily groups after a period of 12 months. The mean percentage change in lumbar spine BMD was 3.5% (95% CI 3.15%–3.93%) in the monthly group and a 3.4% (95% CI 3.03%–3.82%) in the daily group. The difference between the two groups was –0.1% (95% CI –0.51%–0.27%). These results indicated that the once monthly regimen was noninferior to the daily regimen. There was also no significant difference between treatment groups in BMD of sites in the proximal femur, and no significant differences in markers of bone turnover at 3, 6, and 12 months.

No difference between the two treatment groups was observed in the incidence of vertebral fractures as determined by morphometric measurement during the first twelve months. Both groups tolerated the drugs well. The percentage of patients who withdrew from treatment as result of an adverse event was 9.5% in the daily group and 8.6% in the once monthly group. The incidence of gastrointestinal (GI) adverse events was similar in both groups. The symptoms of an acute phase reaction was slightly higher in the once monthly group (1.4%) than in the daily group (0.2%). Atrial fibrillation was reported in 0.5% of the daily group and 0.6% of the once monthly group. No one in the study experienced osteonecrosis of the jaw (ONJ).

In the intermittent dosing studies described above, the incidence of clinical nonvertebral fractures reported as adverse events were similar between the treatment groups, however there have been no placebo-controlled studies addressing the antifracture efficacy of once weekly or once monthly dosing regimen.

Fracture data in high risk populations

In 2006, Ringe and colleagues published a one year study in which men with osteoporosis were randomized to risedronate 5 mg daily versus placebo; risedronate was associated with a 60% reduction in the incidence of new vertebral fracture ($p = 0.028$).[32] There is excellent data demonstrating that risedronate can prevent and treat corticosteroid-induced osteoporosis. Patients who received moderate-to-high doses of corticosteroids and risedronate daily for one year had a 70% reduction in vertebral fracture compared to placebo.[33]

Efficacy of risedronate has been studied in several subsets of patients at risk for osteoporosis by Sato and colleagues.[34] A cohort of 280 men 65 years and older poststroke were followed for 18 months. BMD decreased poststroke secondary to immobilization-induced bone resorption and vitamin D deficiency secondary to immobilization. Half of the patients received risedronate during the 18 month period and half received placebo. There were a similar number of falls between the two groups. The RR of hip fracture was 0.19 (95% CI 0.4–0.89). Sato and colleagues also found a significant reduction of hip fracture in elderly female stroke patients in a 12-month, randomized, double-blind placebo trial of risedronate versus placebo. Seven patients sustained hip fractures on the hemiplegic side in the placebo group, and one hip fracture occurred in the risedronate group ($p = 0.0360$; odds ratio = 7.0).[35] These studies document efficacy of residronate on stroke patients despite immobility, falls, and vitamin D deficiency.

Patients with Alzheimer's are another large group at risk for bone loss and falls. Sato and colleagues studied

500 elderly women (mean age 77.7 years) with Alzheimer's. Both the risedronate and placebo groups showed severe 25 hydroxyvitamin D deficiency (average 9.1 ng/ml) with compensatory hyperparathyroidism. There were 24 hip fractures in the control group and 5 hip fractures in the risedronate group (RR 0.28, 95% CI 0.13–0.59). Of note is that both groups received 1000 IU of ergocalciferol and 1200 mg of elemental calcium and were followed for 28 months.[36]

BMD is also compromised in Parkinson's disease secondary to immobilization-induced bone resorption and hypovitamin D with compensatory hyperparathyroidism. Sato and colleagues followed 121 patients with Parkinson's for two years. All patients received vitamin D2 1000 IU, Nine patients sustained a hip fracture in the placebo group and three patients had hip fractures in the risedronate group with a RR reduction of 0.33 (95% CI 0.09–1.20).[37]

Safety

In general, there is a good safety profile for bisphosphonates. The most common tolerability issues have been upper gastrointestinal symptoms, influenza-like illnesses, and rarely, ONJ and uveitis. Atrial fibrillation has been reported both with zolendronic acid and alendronate, but not with risedronate to date.

Taggart and colleagues pooled nine multicenter, randomized placebo controlled studies of risedronate to review the frequency of upper GI events with risedronate. Sixty percent of patients had a history of GI tract disease, 38.7% had active GI tract disease, and 20.5% used antisecretory drugs during the studies. Sixty-three percent used aspirin and/or nonsteroidal anti-inflammatory drugs during the studies. Upper GI adverse events were reported by 29.6% of patients in the placebo arm compared with 29.8% in the risedronate arm. In addition, endoscopy performed in 349 patients demonstrated no significant difference among the two treatment groups.[38] Harris and colleagues did a study comparing daily and weekly risedronate and similar prevalence of gastrointestinal adverse events among treatment groups.[39]

Osteonecrosis of the jaw is defined as the presence of nonhealing exposed bone in the maxillofacial region which has not healed within eight weeks and in whom there was no history of radiation therapy to the area. Only the maxilla and mandible appear to be susceptible. Pazianis and colleagues performed a literature review to help further clarify the connection between bisphosphonate use and risk of ONJ. Of the eleven publications reported in the review only 26 cases of ONJ were reported.[40] Etminam and colleagues studied a cohort of 87,837 elderly cardiovascular patients who were each on an oral bisphosphonate. The adjusted RR for ONJ among all bisphosphonate users was 2.87 (95% CI 1.71–5.05). The adjusted RR for alendronate, etidronate, and risedronate were 2.87 (95% CI 1.46–5.67), 2.43 (95% CI 1.05–5.62), and 3.34 (95% CI 1.04–10.67). Of interest, is that there were no significant differences in RR of ONJ among current users (recent drug exposure within 90 days) and past users (drug exposure between 91–365 days before diagnosis).[41] Marx and colleagues in the *Journal of Oral and Maxillofacial Surgery* compared details from 30 consecutive cases of ONJ from oral bisphosphonates with 116 cases from intravenous bisphosphonates. In both groups, 50% occurred spontaneously and 50% resulted from an oral surgical procedure, mostly tooth removals. There was a direct exponential relation between the size of the exposed bone and the duration of oral bisphosphonate use. Notably, oral bisphosphonate-induced osteonecrosis was less frequent, less severe, and more responsive to treatment than intravenous-induced osteonecrosis.[42] According to the American Society for Bone and Mineral Research Task Force on Bisphosphonate-Associated ONJ[43] and the American Dental Association Council on Scientific Affairs,[44] actions that may reduce the risk of ONJ in patients about to begin or are currently using bisphosphonates include maintenance of good oral hygiene and regular dental care.

Renal side effects have also been studied, given that bisphosphonates are cleared by the kidney. Miller and colleagues pooled results from nine clinical trials, revealing no significant differences in incidences of renal toxicity between daily risedronate and placebo with baseline renal function being the same between the two groups. Risedronate was found to have no effect on specific renal function or general adverse events across mild, moderate, and severe age-related renal dysfunction.[43] Case reports of uveitis and scleritis have been reported with bisphophonates, mostly alendronate. The ocular events occurred rapidly after treatment and resolved upon cessation.[44] Finally, viral-like illness has been associated with all the bisphosphonates. These symptoms are generally self-limiting, lasting up to 2–3 days and do not recur with subsequent dosing.[45]

Conclusions

There are numerous clinical trials demonstrating the efficacy of risedronate in reducing the risk of vertebral, nonvertebral, and hip fracture in postmenopausal women, men with osteoporosis, men and women with steroid-induced osteoporosis and in subsets of patients with immobility

diseases at high risk for falls. This antifracture efficacy persists over time (seven years) and long term treatment with risedronate is well tolerated. Dosing frequency influences compliance among patients. Risedronate daily, weekly, and monthly have similar BMD changes in the spine and hip, similar changes in markers of bone turnover, and morphometric vertebral fractures. Given the high morbidity and mortality that most fragility fractures carry, treatment with risedronate in the appropriate osteoporotic patient is warranted.

Disclosure

The author reports no conflicts of interest in this work.

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