REVIEW

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Role of alendronate and risedronate in preventing and treating osteoporosis

ABSTRACT

Alendronate and risedronate, the two oral bisphosphonates approved in the United States for preventing and treating osteoporosis, have never been compared in direct head-to-head trials, but they appear to have similar pharmacokinetics, drug interactions, adverse effect profiles, and efficacy. Alendronate, however, can be given as a once-weekly dose, whereas risedronate is not yet available in this dosage form. On the other hand, alendronate is not approved for preventing glucocorticoid-induced osteoporosis, whereas risedronate carries this indication.

KEY POINTS

Both alendronate and risedronate have been found effective in placebo-controlled trials in preventing and treating osteoporosis.

Alendronate and risedronate are generally well tolerated as long as they are taken appropriately to avoid upper gastrointestinal adverse effects.

Alendronate is slightly more expensive than risedronate; however, the once-weekly form of alendronate may enhance patient compliance and tolerability enough to offset the higher cost.

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GIVEN THE SIMILARITIES between alendronate (Fosamax) and risedronate (Actonel), the only two bisphosphonates approved for treating and preventing osteoporosis in the United States, how should clinicians decide which to use in a given patient?

Alendronate and risedronate have similar mechanisms of action, pharmacokinetics, drug interaction profiles, and administration guidelines. Additionally, evaluation of individual drug studies indicates comparable efficacy between the two agents.

The decision as to which bisphosphonate to prescribe for osteoporosis will be influenced by differences in their adverse event profiles (which are being assessed in ongoing trials) and dosing regimens (once a week vs once a day).

RANGE OF TREATMENTS

A variety of nonpharmacologic and pharmacologic interventions are available for preventing and treating osteoporosis. Adequate intake of calcium and vitamin D, regular exercise, smoking cessation, and limiting alcohol intake are recommended initially. Drug treatment options include estrogen replacement, raloxifene, calcitonin, calcitriol, and bisphosphonates (currently only alendronate and risedronate).

INDICATIONS FOR BISPHOSPHONATES

Risedronate is approved by the US Food and Drug Administration (FDA) for preventing and treating postmenopausal osteoporosis and glucocorticoid-induced osteoporosis and for treating Paget disease of the bone.

Alendronate is also FDA-approved for treating Paget disease, for preventing and

TABLE 1

Studies of alendronate and risedronate in preventing postmenopausal osteoporosis

Studies with risedronate

Investigators: Hooper et al[2]
Patients: 383 postmenopausal women 6 to 35 months after onset of menopause
Treatments: Placebo, risedronate 2.5 mg once daily, or risedronate 5.0 mg once daily for 2 years, in addition to 1 g once daily of calcium; prior or current estrogen use was not recorded
Results: Increased bone mineral density in the lumbar spine, femoral neck, and trochanter with 5.0 mg/day vs baseline ($P < .05$) and vs placebo ($P < .05$)
Adverse effects: Similar incidence of esophagitis and esophageal lesions in all three treatment groups

Investigators: Fogelman et al[3]
Patients: 543 postmenopausal women, onset of menopause within 2 years
Treatments: Placebo, risedronate 2.5 mg once daily, or risedronate 5.0 mg once daily for 2 years
Results: Increased bone mineral density in the lumbar spine, femoral neck, and trochanter with risedronate 5.0 mg/day vs baseline (P not reported) and vs placebo ($P < .001$)
Adverse effects: Similar in the risedronate and placebo groups, even in patients with previous or active GI disease

Study with alendronate

Investigators: McClung et al[4]
Patients: 447 postmenopausal women 6 to 36 months after onset of menopause who could have taken estrogen in the past year
Treatments: Placebo or alendronate 1 mg, 5 mg, 10 mg, or 20 mg once daily for 3 years
Results: Increased bone mineral density in the femoral neck and in the total hip with alendronate 5 mg/day vs baseline ($P < .05$); increased bone mineral density in the lumbar spine, femoral neck, and trochanter with alendronate 5 mg/day vs placebo ($P < .001$)
Adverse effects: Similar to placebo for all alendronate dosages

Alendronate and risedronate should be taken at least 30 minutes before food

treating postmenopausal osteoporosis, and for treating glucocorticoid-induced osteoporosis—but not for *preventing* glucocorticoid-induced osteoporosis.

MECHANISM OF ACTION

The mechanism of action of bisphosphonates is not fully understood. Experimental and clinical studies show that at the tissue level they inhibit bone resorption and bone turnover without directly suppressing bone formation, resulting in increased bone mass and mineralization.

Some experts suggest that bisphosphonates work by inhibiting osteoclast formation, recruitment, and activity, or by reducing the life span of osteoclasts by inducing apoptosis.

Bisphosphonates may also act intracellularly, by inhibiting enzymes in the cholesterol metabolism pathway, protein-tyrosine phosphatases, or osteoclast vacuolar H^+,K^+-transporting adenosine triphosphatase. To date, however, we have no evidence of receptor-mediated bisphosphonate action.[1]

PHARMACOKINETICS: LOW ABSORPTION, NO METABOLISM, RENAL EXCRETION

The mean oral bioavailability of both alendronate and risedronate is very low and is reduced even further when taken with food, requiring that patients take these drugs at least 30 minutes before the first food, beverage (other than water), or medication of the day.

Upon absorption, the bisphosphonates are distributed into the bone. We have no evidence of systemic metabolism of alendronate or rised-

TABLE 2

Studies of alendronate and risedronate in treating postmenopausal osteoporosis

Studies with risedronate

Investigators: Harris et al[5]
Patients: 2,458 postmenopausal women with one or more vertebral fractures and no estrogen use in the past month
Treatments: Placebo or risedronate 2.5 mg once daily or risedronate 5.0 mg once daily for 3 years
Results: Incidence of new vertebral fractures 11.3% with risedronate 5 mg/day vs 16.3% with placebo ($P = .003$); incidence of nonvertebral fractures 5.2% with risedronate 5 mg/day vs 8.4% with placebo ($P = .02$); increase in bone mineral density in the lumbar spine, femoral neck, and trochanter with risedronate 5 mg/day vs baseline ($P < .05$) and vs placebo ($P < .05$)
Adverse effects: Similar incidence of upper GI events in risedronate and placebo groups

Investigators: Reginster et al[6]
Patients: 1,226 postmenopausal women with two or more vertebral fractures and no estrogen use within the past 3 months
Treatments: Placebo, risedronate 2.5 mg once daily, or risedronate 5.0 mg once daily for 3 years
Results: Incidence of new vertebral fractures 18% with risedronate 5 mg/day vs 29% with placebo ($P < .001$); incidence of nonvertebral fractures 10.9% with risedronate 5 mg/day vs 16% with placebo ($P = .06$); bone mineral density in the lumbar spine, femoral neck, and trochanter increased with risedronate 5 mg/day vs baseline ($P < .05$) and vs placebo ($P < .001$)
Adverse effects: Similar incidence of adverse GI effects with risedronate vs placebo

Study with alendronate

Investigators: Black et al[7]
Patients: 2,027 postmenopausal women with one or more vertebral fractures and no estrogen use within the past 6 months
Treatments: Alendronate 5 mg once daily (later increased to 10 mg once daily) or placebo for 3 years
Results: Incidence of vertebral fractures 8% with alendronate 10 mg/day vs 15% with placebo ($P < .001$); incidence of nonvertebral fractures 11.9% with alendronate 10 mg/day vs 14.7% with placebo ($P = .063$); increased bone mineral density in the lumbar spine, femoral neck, total hip, and trochanter in the alendronate 10 mg/day group vs placebo ($P < .001$)
Adverse effects: No significant differences in upper GI events between treatment and placebo groups

Bisphosphonates are contraindicated in patients with hypocalcemia

ronate. About 50% of both drugs is excreted unchanged in the urine within 24 to 72 hours.

EFFICACY IN CLINICAL TRIALS

To date, no clinical trial has directly compared the efficacy of alendronate and risedronate in osteoporosis treatment and prevention. Nevertheless, placebo-controlled studies of each agent individually indicate that both are effective and well tolerated in preventing postmenopausal osteoporosis (TABLE 1),[2–4] treating postmenopausal osteoporosis (TABLE 2),[5–7] and in glucocorticoid-induced osteoporosis (TABLE 3).[8–10]

CONTRAINDICATIONS

Alendronate and risedronate are contraindicated in patients with:

- Hypocalcemia
- Known hypersensitivity to any component of the product
- Inability to stand or sit upright for at least 30 minutes
- Abnormalities of the esophagus that delay esophageal emptying, such as stricture or achalasia
- Renal impairment (creatinine clearance < 30 mL/minute for risedronate or < 35 mL/minute for alendronate).

TABLE 3

Studies of alendronate and risedronate in preventing and treating glucocorticoid-induced osteoporosis

Studies with risedronate

Investigators: Cohen et al[8]
Patients: 224 men and women ages 18 to 65 who had begun long-term prednisone therapy (7.5 mg or more per day) within the past 3 months and had not used estrogen within the past year
Treatments: Risedronate 2.5 mg or 5.0 mg once daily or placebo for 1 year
Results: Significant change in bone mineral density of the lumbar spine in both risedronate groups vs baseline (*P* not recorded); increased bone mineral density in the lumbar spine, femoral neck, and trochanter with risedronate 5 mg/day vs placebo ($P < .001$)
Adverse effects: Similar incidence in all three groups

Investigators: Reid et al[9]
Patients: 290 men and women who had been on long-term prednisone therapy (7.5 mg or more per day) or equivalent for more than 6 months and had not used oral estrogen in the past 6 months
Treatments: Risedronate 2.5 mg or 5.0 mg once daily or placebo for 1 year
Results: Increased bone mineral density in the lumbar spine, femoral neck, and trochanter with risedronate 5 mg/day vs baseline ($P < .001$) and vs placebo ($P < .05$); incidence of vertebral fractures 5% with risedronate 5 mg/day vs 15% with placebo ($P = .042$)
Adverse effects: Similar incidence of upper GI events in the risedronate 5 mg/day and placebo groups

Study with alendronate

Investigators: Saag et al[10]
Patients: 477 men and women who had been taking prednisone (7.5 mg/day or more) or an equivalent for at least 4 months and could have used estrogen
Treatments: Alendronate 5 mg once daily or 10 mg once daily or placebo for 12 months
Results: Increased bone mineral density in the lumbar spine, femoral neck, trochanter, and total body with alendronate 10 mg/day vs baseline ($P < .01$) and vs placebo ($P < .01$)
Adverse effects: No difference in serious adverse events among the three groups; a small increase in nonserious upper GI effects occurred with alendronate 10 mg/day

Avoid using these drugs in pregnant and nursing women

CAUTIONS: CHILDREN, PREGNANCY, LACTATION

Alendronate and risedronate have not been tested in children younger than 18 years.

In pregnancy, both drugs are rated as risk category C—ie, adverse fetal effects have been shown in animals, but no human data are available. In animal studies, neonates born to mothers receiving alendronate or risedronate demonstrated decreased body weight and incomplete ossification of vertebral, sternal, and skull bones. Hypocalcemia and increased mortality in pregnant rats were also observed. Therefore, alendronate and risedronate should be used during pregnancy only if the potential benefit justifies the potential risks to the mother and fetus.

It is not known if alendronate and risedronate are excreted in human milk. Therefore, caution should be exercised when giving either drug to nursing women.

HOW COMMON ARE UPPER GI ADVERSE EFFECTS?

Bisphosphonate-induced upper GI adverse events are commonly cited, but the risk may be overstated and more associated with inappropriate administration. The probable mechanism for such effects is local irritation.

Another possibility is that people with osteoporosis have a high incidence of upper GI complaints even without taking bisphosphonates. Indeed, in clinical trials, similar numbers of patients receiving placebo report-

ed upper GI adverse effects as did patients receiving active drug.

Miller et al[11] addressed this issue in a placebo-controlled trial of alendronate rechallenge in 172 postmenopausal women with osteoporosis, all of whom had stopped taking alendronate because of adverse upper GI events that occurred while taking the drug. After 8 weeks of rechallenge therapy, 14.5% of patients receiving alendronate and 17.3% of patients receiving placebo had stopped treatment because of upper GI complaints, including abdominal pain (29.6%), acid regurgitation (25.9%), nausea (18.5%), and gastroesophageal reflux (11.1%). The investigators suggested that upper GI complaints reported during alendronate therapy reflected a high background incidence of upper GI complaints rather than an adverse effect of alendronate.[11]

In another study, conducted by Adachi et al,[12] 66 postmenopausal women who had previously stopped taking alendronate because of upper GI adverse effects received either risedronate 5 mg daily or placebo. After 3 months, 16.1% of patients had stopped taking placebo, compared with 11.4% of patients receiving risedronate. The investigators concluded that risedronate is as well tolerated as placebo in patients who cannot tolerate alendronate.

Are there any differences in GI adverse effects?

Lanza et al[13] assessed the effects of alendronate and risedronate on the incidence of gastric ulcers and on the esophageal and gastroduodenal mucosa in 515 postmenopausal women age 40 and older. Patients received either risedronate 5 mg/day or alendronate 10 mg/day for 14 days, while abstaining from alcohol, smoking, and nonsteroidal anti-inflammatory drugs.

Gastric ulcer, defined as a break of at least 3 mm in the gastroduodenal mucosa extending through the muscularis mucosa, was observed endoscopically in 4.1% of the risedronate group vs 13.2% of the alendronate group ($P < .001$). The investigators concluded that at doses used for osteoporosis treatment, risedronate was associated with a significantly lower incidence of gastric ulcers than alendronate.

However, this study had several drawbacks: it was a short-term study in healthy postmenopausal women and did not include a placebo group to determine the expected risks of gastric ulceration without intervention. The clinical relevance of the small asymptomatic ulceration observed remains unclear.[14]

Higher doses tested. Lanza et al[15] also assessed the potential of alendronate and risedronate to cause endoscopically observed upper GI mucosal irritation, using the highest approved doses (ie, those used in the treatment of Paget disease) and a scale for scoring mucosal erosions.

After a 28-day trial of alendronate 40 mg a day, risedronate 30 mg a day, placebo, or placebo with aspirin 650 mg four times a day for the last 7 days, patients taking risedronate and alendronate had comparable gastric and duodenal erosion scores, and these scores were significantly lower than those in patients taking aspirin.[15] Esophageal erosion scores were comparable in all groups.

However, gastric ulcers (defined as larger, deeper endoscopic erosions) occurred in 3% of patients taking risedronate or alendronate, in 60% of patients taking aspirin, and in none of the patients in the placebo group. Adverse GI effects were reported by 12% in the alendronate group, 15% in the risedronate group, 35% in the aspirin group, and 22% in the placebo group.

Upper GI adverse effects were similar to those of placebo

The investigators concluded that alendronate and risedronate are generally well tolerated and that they pose a very low risk for clinically important gastric irritation, even at the highest dosages used.

MINIMAL DRUG INTERACTIONS

Neither risedronate nor alendronate induces or inhibits the cytochrome P450 enzyme system, so interaction with other drugs is minimal. However, clinicians should note the following:

- Co-administration of calcium supplements, antacids, or oral medications with divalent cations interfere with absorption of risedronate and alendronate
- The concomitant use of aspirin and high-dose alendronate should be avoided because of an increased incidence of upper GI adverse events in clinical trials.

TABLE 4

Oral dosing recommendations for alendronate and risedronate

INDICATION	ALENDRONATE	RISEDRONATE
Postmenopausal osteoporosis		
Prevention	5 mg once a day OR 35 mg once a week	5 mg once a day
Treatment	10 mg once a day OR 70 mg once a week	5 mg once a day
Glucocorticoid-induced osteoporosis		
Prevention	5 mg once a day*	5 mg once a day
Treatment	5 mg once a day OR 10 mg once a day†	5 mg once a day
Paget disease	40 mg once a day for 6 months	30 mg once a day for 2 months

*Not FDA-approved for this indication
†If the patient is postmenopausal and is not taking estrogen

TABLE 5

Average wholesale prices for alendronate and risedronate

PRODUCT	PER TABLET	PER MONTH
Alendronate		
5 mg	$2.12	$63.60*
10 mg	$2.12	$63.60*
35 mg	$14.82	$59.27†
40 mg	$5.30	$159.00‡
70 mg	$14.82	$59.27†
Risedronate		
5 mg	$1.95	$58.50*
30 mg	$13.78	$413.40‡

*Taken once daily for osteoporosis prevention or treatment
†Taken once a week for osteoporosis prevention or treatment
‡Taken once daily for Paget disease

PRICES FROM 2001 DRUG TOPICS RED BOOK. MONTVALE, NJ: MEDICAL ECONOMICS COMPANY, 2001.

Avoid giving high-dose alendronate with aspirin

DOSAGE

TABLE 4 lists the dosing recommendations for risedronate and alendronate. The drugs should be given orally, at least 30 minutes before the first food or drink of the day other than water. The drugs should be swallowed while the patient is in an upright position and should be taken with a full glass of water. Patients should not lie down for 30 minutes after taking risedronate or alendronate.

Once-weekly dosing

Of note, Merck, Inc. recently received FDA approval to market two new dosage strengths of alendronate for once-weekly dosing: a 35-mg tablet for the prevention of postmenopausal osteoporosis and a 70-mg tablet for the treatment of osteoporosis.

This modified dosing schedule for treatment is based on a recent study by Schnitzer et al[16] comparing the efficacy and safety of oral doses of alendronate 70 mg once a week (n = 519), 35 mg twice a week (n = 369), and 10 mg once every day (n = 370). In a 1-year, double-blind, multicenter study of postmenopausal women with osteoporosis, all three regimens produced similar increases in bone mineral density at the lumbar spine, total hip, femoral neck, trochanter, and total body. All three regimens were well tolerated with no statistically significant differences in the most commonly reported upper GI events, including abdominal pain, nausea, dyspepsia, and acid regurgitation. Also, a trend towards a lower incidence of esophageal, gastric, or duodenal adverse effects was observed with once-a-week and twice-a-week dosing vs daily dosing. The authors concluded that alendronate 70 mg once a week is a more convenient alternative to daily dosing and may enhance compliance.

Given the apparent advantages of once-weekly alendronate dosing, Woodson et al[17] reported a trial of risedronate 30 mg once a week for 12 months in 13 postmenopausal women with osteoporosis who did not tolerate FDA-approved therapies. Increases in bone mineral density from baseline were seen in the lumbar spine, femoral neck, and total hip, and the treatment was well tolerated. Statistical analysis was not available.

COST

TABLE 5 compares the average wholesale prices of alendronate and risedronate in dosages used for osteoporosis prevention and treatment. Risedronate is slightly less expensive. However, improved patient compliance and tolerability of the once-weekly form of alendronate could offset this cost difference. Further studies are necessary to directly compare adverse effects of risedronate and alendronate and to clinically evaluate the modified once-weekly dosing regimen.

REFERENCES

1. **Rodan GA.** Mechanism of action of bisphosphonates. Annu Rev Pharmacol Toxicol 1998; 38:375–388.
2. **Hooper M, Ebeling P, Roberts A, et al.** Risedronate prevents bone loss in early postmenopausal women [abstract]. Calcified Tissue International 1999 (suppl 1): Abstract P-80.
3. **Fogelman I, Ribot C, Smith R, et al.** Risedronate reverses bone loss in postmenopausal women with low bone mass: results from a multinational, double-blind, placebo-controlled trial. J Clin Endocrinol Metab 2000; 85:1895–1900.
4. **McClung M, Clemmesen B, Daifotis A, et al.** Alendronate prevents postmenopausal bone loss in women without osteoporosis. Ann Intern Med 1998; 128:253–261.
5. **Harris ST, Nelson B, Genant HK, et al.** Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis. JAMA 1999; 282:1344–1352.
6. **Reginster J, Minne HW, Sorensen OH, et al.** Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Osteoporos Int 2000; 11:83–91.
7. **Black DM, Cummings SR, Karpf DB, et al.** Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Lancet 1996; 348:1535–1541.
8. **Cohen S, Levy RM, Keller M, et al.** Risedronate therapy prevents corticosteroid-induced bone loss: a 12-month, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis Rheum 1999; 42(11):2309–2318.
9. **Reid D, Hughes R, Laan RF, et al.** Efficacy and safety of daily risedronate in the treatment of corticosteroid-induced osteoporosis in men and women: a randomized trial. J Bone Miner Res 2000; 15:1006–1013.
10. **Saag KG, Emkey R, Schnitzer TJ, et al.** Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis. N Engl J Med 1998; 339:292–299.
11. **Miller PD, Woodson G, Licata AA, et al.** Re-challenge of patients who had discontinued alendronate therapy because of upper gastrointestinal symptoms. Clin Ther 2000; 22:1433–1442.
12. **Adachi JD, Adami S, Miller PD, et al.** Tolerability of risedronate in alendronate-intolerant postmenopausal women (abstract). ACR 64th Annual Scientific Meeting and ARHP 35th Annual Scientific Meeting, October 28-November 2, 2000, Philadelphia.
13. **Lanza FL, Hunt RH, Thomson AB, Provenza JM, Blank MA.** Endoscopic comparison of esophageal and gastroduodenal effects of risedronate and alendronate in postmenopausal women. Gastroenterology 2000; 119:631–638.
14. **Leder BZ, Kronenberg HM.** Gastroenterologists and choosing the right bisphosphonate. Gastroenterology 2000; 119:866–871.
15. **Lanza F, Schwartz H, Sahba B, et al.** An endoscopic comparison of the effects of alendronate and risedronate on upper gastrointestinal mucosa. Am J Gastroenterol 2000; 95:3112–3117.
16. **Schnitzer T, Bone HG, Crepaldi G, et al.** Therapeutic equivalence of alendronate 70 mg once-weekly and alendronate 10 mg daily in the treatment of osteoporosis. Alendronate once-weekly study group [abstract]. Aging 2000; 12:1–12.
17. **Woodson G.** Once-weekly risedronate therapy. Osteoporos Int 2000; 11:550.

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