

# Risedronate

## A Clinical Review

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**Background:** Risedronate sodium has recently been approved for the prevention and treatment of postmenopausal and corticosteroid-induced osteoporosis.

**Methods:** Studies of risedronate were obtained from the MEDLINE database (1966 to the present) of references using *risedronate*, *risedronic acid*, *osteoporosis*, and *human subject* as keywords. Additional references were sought from the reference lists of the articles obtained.

**Results:** Nine randomized controlled trials and 7 other clinical trials were obtained. In postmenopausal women with normal bone density, risedronate increases lumbar spine bone density and preserves femoral neck density. In postmenopausal women with prior vertebral fracture, risedronate decreases new vertebral and nonvertebral fracture incidence. In patients who experienced breast cancer and who have chemotherapy-induced menopause, risedronate preserves bone. Risedronate prevents vertebral bone loss in patients beginning long-term corticosteroid therapy. Risedronate decreases pagetic bone pain and induces radiological improvement in pagetic lesions. Risedronate in-

duces normalization of biochemical abnormalities and may be more effective than etidronate disodium for Paget disease. Only one study, a trial in patients with postmenopausal osteoporosis using a low dose (2.5 mg) of risedronate, did not have a positive result. Adverse effects in patients with postmenopausal osteoporosis, breast cancer, and Paget disease and in those taking corticosteroids are similar to those of patients taking placebo, and do not include notable upper gastrointestinal tract adverse event rates or serious adverse events.

**Conclusions:** Risedronate prevents postmenopausal bone loss, decreases fracture in those with established postmenopausal osteoporosis, effectively treats Paget disease, and prevents corticosteroid-induced bone loss. Long-term toxic effects and efficacy, particularly fracture end point data, are unknown. Also undefined are optimal duration of therapy, potential for use in combination with other agents, and direct comparison with other bisphosphonates used for osteoporosis.

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**R**ISEDRONATE SODIUM, also known as NE-58095 or risedronic acid, is an aminobisphosphonate. Its chemical name is 2-hydroxyethylidene-2-(3-pyridinyl)-1,1-bisphosphonate disodium.<sup>1</sup> Risedronate was approved in the United States for the treatment of Paget disease in 1998.<sup>1,2</sup> On April 24, 2000, it was approved in the 5-mg/d dose for the prevention and treatment of corticosteroid-induced and postmenopausal osteoporosis.

The first bisphosphonate is said to have been synthesized in 1897 by Von Baeyer and Hofmann.<sup>3</sup> Since 1962, it has been known that inorganic pyrophosphate, a by-product of human physiological reactions, could bind to hydroxyapatite crystals.<sup>4</sup> However, because of gastrointestinal tract hydrolysis, the pyrophosphates were inactive when given

orally to laboratory animals. Thus, the diphosphonates, later called bisphosphonates, were developed as more stable analogues of pyrophosphate. Etidronate disodium was the first bisphosphonate to be aggressively studied for the treatment of osteoporosis.<sup>5</sup> However, it interfered with bone mineralization in doses that would be used clinically for the treatment of osteoporosis.<sup>6</sup> More recent agents do not manifest this disadvantageous characteristic.

Bisphosphonates are pyrophosphate analogues in which the oxygen in the P-O-P structure has been replaced with a carbon, yielding a P-C-P structure.<sup>7</sup> The P-C-P structure confers resistance to hydrolysis on exposure to acids or hydrolytic enzymes.<sup>4</sup> One side chain provides affinity to bone mineral, while the other is responsible for the potency of inhibition of osteoclastic activity.<sup>7</sup> A hydroxyl group

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at the R<sub>1</sub> position increases affinity for bone mineral.<sup>4</sup> The R<sub>2</sub> position can be manipulated to enhance potency while preserving the R<sub>1</sub> affinity for bone. (R<sub>1</sub> and R<sub>2</sub> are positions on the carbon atom of the bisphosphonate structure. They represent side chains. R<sub>1</sub> determines the affinity for bone mineral and R<sub>2</sub> is responsible for potency characteristics.)

There are 3 generations of bisphosphonates. Etidronate is a first-generation agent. Alendronate sodium and pamidronate disodium, which are second-generation agents containing a basic primary nitrogen atom in an alkyl chain, are 10- to 100-fold more potent than are etidronate and clodronate. (Although tiludronate does not contain an amino terminal group, it is considered second generation because of the timing of development and potency.) Even more potent are agents containing a tertiary nitrogen, such as the third-generation agent ibandronate. The most potent agents contain a nitrogen atom within a heterocyclic ring, eg, risedronate and zoledronate.<sup>4,5,8</sup>

Bisphosphonates have theoretical advantages over estrogen replacement therapy in that they are bone specific, have minimal adverse effects, and have no known carcinogenic potential.<sup>9</sup> Cellular mechanisms of the bisphosphonates are not yet understood in their entirety. Russell and Rogers<sup>4</sup> have recently reviewed these mechanisms. The bisphosphonate most extensively studied for osteoporosis treatment is alendronate.

In female rats that undergo ovariectomy, risedronate increases connectivity density and total trabecular number, suggesting that it may help increase bone connectivity in the estrogen-deficiency state.<sup>10</sup> These and other similar findings have caused risedronate to be studied for clinical use in the settings of osteoporosis and Paget disease.

## MATERIALS AND METHODS

A MEDLINE search (1966 to the present) was performed for keywords *risedronate*, *risedronic acid*, *osteoporosis*, and *human subject*. All MEDLINE (1966 to the present)

clinical trials with the keyword *risedronate* or *risedronic acid* were also retrieved. The reference lists from the retrieved articles were reviewed for additional relevant studies.

## RESULTS

In addition to several reviews and animal trials, 16 clinical trials<sup>11-26</sup> of risedronate in humans were retrieved (additional data available from the authors). Of these, 10 were randomized controlled trials.<sup>11-14,21-26</sup> Of the 16 clinical trials, 7 reports<sup>12,15-20</sup> pertained to Paget disease, 3<sup>11,13,14</sup> focused on postmenopausal women with or without preexisting fractures, and 1<sup>21</sup> studied risedronate use in women with breast cancer. Four additional studies<sup>23-26</sup> examined risedronate's properties in healthy volunteers. There was 1 trial<sup>22</sup> of risedronate in the prevention of corticosteroid-induced bone loss.

Dosing for postmenopausal osteoporosis prevention or treatment was 5 mg/d continuously. Dosing for Paget disease ranged from 28- to 84-day cycles. Dosing in the breast cancer survivor study was 30 mg/d for 2 weeks and 10 weeks of no treatment. Dosing in the corticosteroid-induced osteoporosis prevention study was 5 mg/d continuously. Dosing was cyclical for Paget disease, whereas it was continuous for postmenopausal osteoporosis prevention, postmenopausal osteoporosis treatment, and corticosteroid-induced osteoporosis prevention.

The 10 randomized controlled trials were performed on postmenopausal women (n=3),<sup>11,13,14</sup> long-term corticosteroid users (n=1),<sup>22</sup> breast cancer survivors with chemotherapy-induced menopause (n=1),<sup>21</sup> patients with Paget disease (n=1),<sup>12</sup> and healthy volunteers (n=4).<sup>23-26</sup>

Study duration ranged from immediate follow-up of single-dose administration to 3 years.<sup>11</sup> There was one comparative trial.<sup>12</sup>

Five studies<sup>11,13,14,21,22</sup> reported bone mineral density (BMD) effects of risedronate (data available from the authors). Three studies<sup>11,13,22</sup> included fracture outcome data (data available from the authors). Two<sup>11,22</sup> of the 3 reported some extent of antifracture benefit

of daily risedronate therapy. Data are more uniform in showing fracture outcome benefit of the 5-mg dose, compared with the 2.5-mg dose.

Data on safety evaluations in the clinical trials may be obtained from the authors. Overall, risedronate was free of serious adverse effects.

## COMMENT

### POSTMENOPAUSAL OSTEOPOROSIS

Three clinical trials<sup>11,13,14</sup> examined the bone effects of risedronate on postmenopausal women. All were randomized, double-blind, placebo-controlled studies.

A phase 2 study<sup>13</sup> administered 2.5 mg of risedronate in continuous (daily) vs cyclic (risedronate daily for 2 weeks, followed by 10 weeks of placebo) fashion vs placebo in double-blind randomized fashion. The 132 subjects had at least 1, but no more than 4, preexisting vertebral fracture at baseline, and were at least 1 year postmenopausal. Study medication was taken orally 2 hours before bedtime, in the absence of food consumption 2 hours before and afterward. All took a calcium supplement, 1 g/d. After the 2 years of treatment, the trial was extended for 1 year of follow-up, during which calcium, 1 g/d, was taken. Seventy percent completed 3 years of risedronate therapy. The primary efficacy measure was spine BMD, and secondary measures were hip BMD and bone turnover markers. Study findings overall showed lack of effect of risedronate. There were no notable changes in bone turnover markers, nor were there differences between groups in incidence and rate of new vertebral fractures. Adverse events were similar across groups, and none were believed to be causally related to risedronate.<sup>13</sup> This is true even though patients with gastrointestinal tract diseases were not excluded. (Gastrointestinal tract toxic effects have been a concern with past bisphosphonates.) The researchers speculated that perhaps inadequate dosing or absorption explained the lack of efficacy. Subsequent work, there-

fore, made use of higher doses. Vertebral fracture incidence was a secondary outcome, done as part of safety assessment in this study.

A double-blind placebo-controlled study<sup>14</sup> randomized 111 early postmenopausal patients to oral placebo; risedronate, 5 mg/d; or risedronate, 5 mg, given cyclically for 2 years. At baseline, the subjects all had lumbar BMD values within 2 SDs of age-matched mean bone mass values. The cyclic regimen was risedronate, 5 mg/d, for the first 2 weeks of every calendar month, followed by placebo daily for the rest of the month. Patients were stratified according to calcium intake to address the possibility that calcium intake affected response to therapy. The study medication was taken with at least 236.56 mL (8 oz) of water 2 hours before bedtime and 2 hours after a meal. Subjects were told not to take dairy products; vitamins; or calcium-, iron-, magnesium-, or aluminum-containing antacids within 2 hours of taking the study medication. Patients were then followed up for 1 year while not taking treatment. Primary efficacy was change in lumbar spine BMD at 24 months, and other measures included change in proximal femur BMD and bone turnover.

After 24 months, trochanteric bone mass increased by 5.4% in the daily risedronate group, and by 3.3% in the cyclic group, compared with placebo. Lumbar spine BMD increased by 5.7% in the risedronate cyclic group vs placebo. Bone mass was maintained at the femoral neck in the 2 risedronate groups, whereas 2.4% loss occurred with placebo. At the end of the third year, ie, at the end of the 1-year observation period while subjects were not taking treatment, lumbar BMD was lower than at baseline in all 3 groups. The 5-mg/d dose thus increased BMD and the 5-mg cyclic dose prevented bone loss in these early menopausal women with normal BMD.<sup>14</sup> As with the prior study,<sup>13</sup> it is unfortunate that vertebral fracture incidence was part of the safety assessment, as opposed to primary fracture outcome. A strength of the study was its inclusion of patients with a history of gastrointestinal tract disease.

The Vertebral Efficacy With Risedronate Therapy Study<sup>11</sup> randomized 2458 ambulatory postmenopausal women younger than 85 years with at least 1 baseline vertebral fracture to risedronate, 2.5 vs 5.0 mg, vs placebo for 3 years. The protocol advised consumption of the medication once daily on an empty stomach, 30 to 60 minutes before breakfast, with water, and while remaining in the upright position for 1 hour afterward. All subjects received calcium, 1000 mg/d, and those with low serum 25-hydroxyvitamin D levels also received cholecalciferol (vitamin D) up to 500 IU/d. Patients were stratified according to number of baseline vertebral fractures, and randomly assigned within each stratum to each study group. Study outcomes included incidence of new vertebral fractures (proportion of subjects with  $\geq 1$  incident fractures in 3 years). The 2.5-mg arm of the study was stopped after 1 year because of other trials<sup>13</sup> showing relative lack of effectiveness of the 2.5-mg dose. The study had at least 90% power to detect 40% reduction in vertebral fracture risk. Bone turnover markers and radiographically confirmed nonvertebral fractures (of the clavicle, humerus, wrist, pelvis, hip, or leg, either related or unrelated to trauma) were other outcomes.

The 5-mg dose decreased cumulative new vertebral fracture incidence by 41% compared with placebo. The cumulative incidence of nonvertebral fractures in 3 years was decreased by 39% vs placebo. Lumbar spine, femoral neck, femoral trochanter, and radius midshaft BMD measurements were all increased more in the 5-mg group than in the placebo group. Bone biopsies performed at selected study centers revealed bone to be histologically normal. The study included patients with a history of gastrointestinal tract disease. Placebo and risedronate safety levels were similar.<sup>11</sup> The study was well designed and included a much larger sample than did the other risedronate studies.

In summary, based on randomized, double-blind, placebo-controlled trials of 2 to 3 years' duration, risedronate is efficacious in preventing bone loss in postmeno-

pausal women with normal bone density, and in decreasing fractures in patients with established ( $\geq 1$  preexisting vertebral fractures) osteoporosis. Risedronate was well tolerated in all studies. There are only a few studies with fracture outcome, due at least in part to inadequate study size and duration, with resultant inadequate statistical power.

## PAGET DISEASE

Seven clinical trials<sup>12,15-20</sup> of risedronate for Paget disease were retrieved.

Preliminary human testing of risedronate in Paget disease<sup>15</sup> encouraged further investigation. An open-label study<sup>20</sup> of patients with severe Paget disease of bone (alkaline phosphatase level 6 times the upper limit of normal) assigned 12 men and 8 women, aged 60 to 87 years, to receive risedronate, 30 mg/d, for 84 days, followed by observation for 112 days without treatment.<sup>27</sup> The cycle was repeated in patients who did not have normalization of the alkaline phosphatase level or who had an increase of 25% or more in the alkaline phosphatase level. Primary efficacy end points were percentage change in baseline alkaline phosphatase level and excess urinary hydroxyproline/creatinine levels. The secondary efficacy measure was pain due to Paget disease. All patients responded during the initial course of therapy. Most patients had a decrease in alkaline phosphatase level with risedronate therapy. In 65% of the patients, the alkaline phosphatase level normalized. There was progressive decline and elimination of pagetic bone pain, to the extent that 0% of the patients had pain at re-treatment day 56. Thereafter, all patients remained free of pain for the duration of the study. Three-month courses of treatment with risedronate thus safely reduced biochemical disease activity indexes, normalized the alkaline phosphatase level in most of these patients with severe Paget disease, and significantly reduced pagetic bone pain.<sup>20</sup> The study was well done but only had a few patients.

In another open-label study,<sup>19</sup> 8 male and 5 female patients with se-

vere Paget disease (alkaline phosphatase level 17 times the upper limit of normal) were given risedronate, 30 mg/d, for 8 weeks and then followed up for 16 weeks without treatment. Patients who did not attain normal alkaline phosphatase levels after treatment received another 8-week course. The primary outcome measure was serum alkaline phosphatase percentage change from baseline. All patients had a decrease of at least 77% in alkaline phosphatase level vs baseline. Urinary hydroxyproline/creatinine levels also decreased with treatment.<sup>19</sup> Again, the study appears to have been well performed but is small. In addition, pain outcomes were not reported.

Siris et al<sup>18</sup> performed an open-label multicenter study in 102 men and 60 postmenopausal women with moderate to severe Paget disease of bone, ie, a serum alkaline phosphatase level 3 times the upper limit of normal. Patients received risedronate, 30 mg/d, orally for 84 days, followed by 112 days without treatment. Patients whose alkaline phosphatase level did not respond adequately, as defined as lack of normalization or increase by 25% or more, received another 196-day cycle of treatment. Primary efficacy end points were the percentage change from baseline in serum alkaline phosphatase level and urinary hydroxyproline-creatinine ratio. The secondary end point was pain due to Paget disease. Risedronate decreased pagetic bone pain. On day 196, 42% of the subjects had no pagetic pain. Normalization of the alkaline phosphatase level was observed in many (53.8%) of the patients with the study protocol, and repeated administration was beneficial.<sup>18</sup> The trial was larger than others. An additional benefit of the trial was the inclusion of radiological assessment. In a subgroup (16 men and 10 women) of the study population, radiological improvement of pagetic lesions occurred at all skeletal sites.<sup>16</sup> Moreover, it showed risedronate to be devoid of deleterious effect on osteolytic lesions of weight-bearing bones. Risedronate treatment was thus highly effective for improving bone lesions, without deleterious effects on osteolytic le-

sions in weight-bearing bones.<sup>16</sup> This report adds another dimension to the pain and biochemical improvement previously reported with risedronate.

An open-label, dose-escalation study<sup>17</sup> of 62 patients, aged 18 to 75 years, with severe Paget disease of bone (alkaline phosphatase level >3 times the upper limit of normal) compared 3 doses (10, 20, and 30 mg/d) of risedronate. Study medication was taken with 118.28 mL (4 oz) of water 2 hours before or after any meal. Primary efficacy was percentage change of serum alkaline phosphatase level. Patients were advised to use calcium carbonate supplements as necessary to maintain daily calcium intake of at least 700 mg. There was a dose-response relation, such that after 28 days of treatment, the 30-mg dose benefited most patients. Time to response was also shorter with the 30-mg dose. Histological analysis found that the bone formed during therapy was normal, without characteristics of Paget disease and without osteomalacia. Parathyroid levels declined during therapy. Although all 3 doses were effective, safe, and tolerable, the researchers found the 30-mg/d single dose to be the most effective.<sup>17</sup> The study had the advantage of comparing multiple doses, ie, establishing a dose-response relation, and of including histologic bone assessment.

In the only comparative study,<sup>12</sup> 123 patients, aged 18 to 85 years, with Paget disease of bone (serum alkaline phosphatase level  $\geq 2$  times the upper limit of normal) were randomized in double-blind fashion to risedronate, 30 mg/d, for 2 months or etidronate, 400 mg/d, for 6 months. The main outcome of interest was response of alkaline phosphatase level. A higher percentage of patients taking risedronate (73%) than etidronate (15%) manifested normalization of the alkaline phosphatase level. Risedronate caused a more rapid normalization of the alkaline phosphatase level. *Relapse rates*, defined as an increase of 50% or greater above the lowest serum alkaline phosphatase level, were lower in the risedronate vs the etidronate group. At month 6, a higher percentage of patients taking risedro-

nate (77%) vs etidronate (11%) had normalization of serum alkaline phosphatase. Pain reduction was significant in the risedronate, but not the etidronate, group. Overall, although etidronate was effective, risedronate had the advantages of shorter duration of therapy, higher rates of (and longer-lasting) remission, and significant pain reduction, even in patients who had not responded adequately to etidronate in the past.<sup>12</sup> The adverse effect profiles of the 2 drugs were similar. The study was unique in establishing the efficacy of risedronate in direct comparison with a well-established treatment.

Therefore, all the available data suggest efficacy of cyclical risedronate, 30 mg/d, in relieving various signs and symptoms of Paget disease of bone, and hint at a possible advantage over etidronate in this setting.

#### PATIENTS WITH BREAST CANCER

Fifty-three white women, aged 36 to 55 years, with breast cancer and artificial (induced) menopause were randomized to receive risedronate or placebo.<sup>21</sup> Patients taking tamoxifen citrate were stratified into both groups. Risedronate and placebo were taken in cyclic fashion. Risedronate dosing was 30 mg/d for 2 weeks, followed by 10 weeks without the drug, for 2 years. The study medication was taken with water 2 hours before lunch. Patients were told to avoid dairy products, vitamins, or antacids containing calcium, iron, magnesium, or aluminum within 2 hours of dosing. They were not to lie down for at least 1 hour following ingestion. Further observation followed for 1 year. Primary efficacy was lumbar and hip BMD measurements.

While the placebo group experienced a decrease in lumbar and hip BMD values, BMD increased in the risedronate group. Moreover, accrued BMD was lost on withdrawal of treatment. At 2 years, there was a 2.5% and 2.6% difference between groups at the lumbar and femoral neck sites, respectively.<sup>21</sup> Results were similar at the trochanter. Tamoxifen itself partly reduced bone loss in the analysis by stratum. Rise-

dronate was well tolerated, without laboratory abnormalities. Thus, risedronate prevented loss of trabecular and cortical bone in this study<sup>21</sup> of patients with breast cancer who experience menopause due to chemotherapy.

### PATIENTS TAKING CORTICOSTEROIDS

One study<sup>22</sup> has examined risedronate use in patients taking concurrent corticosteroids, and it is 1 of the 3 studies<sup>11,13,22</sup> on risedronate that have reported fracture outcome.

A 12-month randomized double-blind study<sup>22</sup> noted the ability of risedronate to prevent corticosteroid-induced bone loss. Men (n=87) and women (n=151 [premenopausal] and n=105 [postmenopausal]), aged 18 to 55 years, who were initiating long-term corticosteroid treatment were randomized to risedronate, 2.5 or 5 mg, or placebo daily for 12 months. Subjects had various rheumatologic, pulmonary, and dermatological indications for corticosteroids. They were considered for the study if they were expected to require prednisone, 7.5 mg/d or more, or equivalent for another 12 months. Medication was to be taken on an empty stomach, 30 to 60 minutes before breakfast, with 236.56 mL (8 oz) of water, and without lying down for 1 hour afterward. All received elemental calcium, 500 mg/d. Cholecalciferol supplements were recommended to subjects who had low serum 25-hydroxyvitamin D<sub>3</sub> levels. Primary outcome was lumbar BMD, and secondary outcomes were proximal femur BMD and vertebral fracture incidence. When the 2.5-mg dose was found to be inadequate in other ongoing research,<sup>13</sup> the 2.5-mg arm was discontinued.

After 12 months, lumbar BMD did not change from baseline in either risedronate group, whereas it decreased in the placebo group.<sup>22</sup> The BMD values of the 5-mg and placebo groups differed by 3.8% at the lumbar, 4.1% at the femoral neck, and 4.6% at the femoral trochanter sites. There was a trend in reduction of vertebral fracture in the 5-mg risedronate group vs the placebo group. The incidence of gastroin-

testinal tract adverse events was similar between the groups, and risedronate was well tolerated.<sup>22</sup> Risedronate therapy thus prevented bone loss in one study of patients beginning long-term corticosteroid therapy. Unfortunately, vertebral and nonvertebral fractures were not primary outcomes.

### PHARMACOKINETIC CHARACTERISTICS

Intestinal absorption of all bisphosphonates is low, ie, 0.5% to 3%. The bioavailability of risedronate in healthy volunteers is 0.63%.<sup>28</sup> Dosing half an hour before breakfast or 2 hours after dinner, as opposed to in the fasting state, decreases the extent of absorption by 55%.<sup>28</sup> In contrast, the extent of absorption is only reduced by 30% if dosing is 1 hour before breakfast.<sup>28</sup>

Risedronate absorption was comparable in 127 healthy volunteers who took the medication 2 hours after a standardized dinner and half an hour before breakfast; however, absorption was significantly (1.4- to 2.3-fold) greater when risedronate was given 1 or 4 hours before a meal.<sup>23</sup> Also, the measured rate of absorption was greater with administration 0.5, 1, or 4 hours before a meal, compared with 2 hours after dinner. The researchers believed that the comparable extent of absorption at 0.5 to 1 hour before breakfast and 2 hours after dinner may give risedronate an advantage of dosing flexibility.<sup>23</sup> Consequently, risedronate is recommended to be taken at least 30 minutes before the first food or drink (other than water) of the day, without lying down for 30 minutes afterward, and with a full glass of plain water in an effort to avoid upper gastrointestinal tract adverse effects.<sup>28</sup>

Avoidance of concomitant ingestion of risedronate with calcium, antacids, or other oral medication that contains divalent cations is prudent, due to these agents' ability to interfere with absorption of risedronate.<sup>28</sup> Studies regarding drug-drug interactions involving risedronate are lacking.

In healthy men, the rate and extent of risedronate absorption are independent of site of administration

along the gastrointestinal tract (ie, stomach, second part of the duodenum, or terminal ileum), and the extent of absorption is not affected by the rate of administration.<sup>24</sup>

A study<sup>25</sup> randomized 3 groups of healthy male (n=61) and female (n=6) volunteers to a single oral dose of 2.5, 5, or 30 mg of risedronate in double-blind fashion. Urinary excretion was found to be dose proportional, as were other pharmacokinetic variables (mean maximum concentration of drug and area under the curve).

Risedronate is excreted unchanged by the kidneys.<sup>28</sup> Dose adjustment in the setting of mild to moderate renal dysfunction is believed to be unnecessary.<sup>8,28</sup> Safety in the setting of hepatic impairment is unknown.

As with other bisphosphonates, after risedronate is administered, most of the dose remains in the skeleton and is later released in the course of skeletal remodeling. Thus, the bone turnover rate determines the amount of drug released from the skeleton.<sup>7</sup> Because of the short circulating half-life, exposure of tissues other than bone to risedronate is minimal. In clinical doses, the bisphosphonates concentrate to significant degrees only at bone, especially inside osteoclasts during active bone resorption. Bisphosphonates decrease osteoclast activity when they enter osteoclasts during bone resorption.

### SAFETY CONSIDERATIONS

In single-dose studies of healthy volunteers, some minor adverse effects were reported. Adverse events were comparable between the 4 different dosage groups (30 mg of risedronate given in different conditions of food intake) in the study by Mitchell et al,<sup>23</sup> with headache, nausea, dizziness, diarrhea, and myalgia being the most common reported adverse events. A small single-dose study<sup>24</sup> of risedronate in healthy men reported headaches and body aches possibly related to risedronate. Single risedronate doses (2.5, 5, and 30 mg) in another study<sup>25</sup> were not associated with serious adverse events. Adverse events were reported by 64%, 82%, and

91% of the patients receiving 2.5, 5, and 30 mg, respectively. The most frequent adverse events were headache and abdominal pain. There were no serious adverse effects. All but one (diarrhea in one subject who took the 30-mg dose) of the adverse events were of mild or moderate severity. One study<sup>26</sup> did not discuss adverse effects.

As previously mentioned, there is no suggestion of an adverse effect of risedronate on bone quality in patients with Paget disease, postmenopausal women, or corticosteroid users. Also, there is no evidence of a deleterious effect on osteolytic lesions in weight-bearing bones, but rather improvement.<sup>16</sup>

The Paget disease studies had a low incidence of adverse effects. In the study by Brown et al,<sup>17</sup> 2 patients taking risedronate had gastrointestinal tract adverse effects that did not cause them to drop out. No adverse events were related to the study drug, and there were no withdrawals due to adverse events, in the trial of Hosking et al.<sup>20</sup>

The comparative study of etidronate (6 months) with risedronate (2 months) in subjects with Paget disease of bone found the adverse effects of the 2 drugs to be similar.<sup>12</sup> Adverse events possibly related to the study drug occurred in 47% of each group. Twenty percent of each group experienced upper gastrointestinal tract adverse events. There were no cases of esophagitis. Eight percent of the etidronate and 6% of the risedronate group withdrew because of adverse events.<sup>12</sup> Small studies<sup>19</sup> of patients with Paget disease found risedronate to be well tolerated. Only one patient stopped treatment. The patient's diarrhea was believed to be treatment related. Brown et al<sup>15</sup> reported mild epigastric discomfort in 3 of 59 patients with Paget disease, but there were no withdrawals for gastrointestinal tract intolerance. Siris et al<sup>18</sup> found no adverse events related to risedronate.

Patients with breast cancer and corticosteroid users tolerate risedronate well. The patients with breast cancer, studied by Delmas et al,<sup>21</sup> who were assigned risedronate had a similar adverse event profile to those taking placebo. Most adverse

events were mild, and there were no severe gastrointestinal tract adverse events. Of 27 patients assigned to risedronate, 4 had mild and 1 had moderate abdominal pain.<sup>21</sup> The incidence of upper gastrointestinal tract events was comparable with risedronate, 2.5 vs 5 mg, vs placebo in the report of Cohen et al<sup>22</sup> of long-term corticosteroid users.

Postmenopausal women have similar overall safety profiles with risedronate and placebo, even considering gastrointestinal tract safety.<sup>11</sup> The study by Mortensen et al,<sup>14</sup> which included healthy early postmenopausal women and which is notable because it did not exclude patients with a history of upper gastrointestinal tract disease, found that risedronate was well tolerated. There was no difference in incidence of adverse effects between risedronate and placebo. Reports of arthralgia were low and similar in the placebo and risedronate groups. There was no increased incidence of abdominal pain or dyspepsia in the risedronate vs placebo group. Clemmesen et al<sup>13</sup> found that the distribution of adverse events was similar across treatment groups, and reported that none of the serious adverse events appeared to be causally related to risedronate.

In summary, the safety data from all of the 6 randomized controlled trials in settings of postmenopausal osteoporosis, breast cancer, corticosteroid use, and Paget disease suggest that the adverse effect profile of risedronate is similar to that of placebo, and does not include any particularly notable upper gastrointestinal tract adverse event rate. In addition, the fact that studies did not exclude patients with a history of such events is optimal for assessment of potential advantages over alendronate and other bisphosphonates.

## FUTURE QUESTIONS

The details of how risedronate and other bisphosphonates exert their antiresorptive activities remain unclear, although relevant work is in progress.<sup>29</sup> Additional research is needed along these lines.

Clinical studies are also needed comparing the bisphosphonates with each other in patients with osteopo-

rosis. Other clinical issues to be resolved are optimal duration of therapy, schedule (cyclic vs continuous), optimal timing of initiation, and use in combination regimens. Perhaps risedronate could be used with other antiresorptive agents, such as estrogen, in an effort to increase bone preservation. For example, recent work<sup>30</sup> suggests that other bisphosphonates can be safely combined with estrogen replacement for added BMD benefit in patients with postmenopausal osteoporosis. Mevastatin, a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, is an even more potent inhibitor of bone resorption *in vivo* than are bisphosphonates.<sup>4</sup> The role of mevastatin in osteoporosis, including whether it can or should be combined with bisphosphonates, remains to be elucidated.

Aside from attempting combination with other antiresorptive agents, which solely stop the loss of bone and do not directly increase bone density, it would be optimal to discover a bone formation inducer that could be used in combination with risedronate.<sup>31</sup> Such candidates for further study include fluoride, bone growth factors, growth hormone, and parathyroid hormone.<sup>31</sup> For example, addition of risedronate to another anabolic hormone, intermittent human parathyroid hormone I<sub>34</sub>, in aged beagle dogs may help protect the cortical and endocortical envelope.<sup>32</sup> Similar research<sup>33</sup> in rats found that addition of risedronate prevented the fast and pronounced endosteal bone resorption and the decrease in mechanical strength that was induced by withdrawal of human parathyroid hormone I<sub>34</sub>.

Prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) has marked anabolic bone effects that are lost on cessation of administration. Female rats treated with risedronate are able to maintain PGE<sub>2</sub>-induced new bone that would have been otherwise lost with discontinuation of PGE<sub>2</sub>.<sup>34</sup> Work<sup>35</sup> in rats that underwent ovariectomy has found that risedronate may prevent trabecular bone loss that characterizes the off period of PGE<sub>2</sub>, thus precluding the need for continuous PGE<sub>2</sub> administration.

Risedronate's role in malignant neoplasms is also under inves-

tigation. Pretreatment of breast and prostatic carcinoma cells with an analogue of risedronate, NE-10244, has been found to inhibit tumor cell adhesion to mineralized and unmineralized extracellular matrices in a dose-dependent manner.<sup>36</sup> In mice, risedronate appears to have the ability to selectively decrease breast cancer burden in bone, suppress progression of established osteolytic lesions, and prevent development of new osteolytic lesions, thereby increasing survival.<sup>37</sup> The question of how these data will influence breast cancer in humans is an exciting line of inquiry.

Because of the poor absorption of bisphosphonates, the optimal method of delivery is the subject of ongoing research. A comparison of the esophageal transit of the film-coated tablet vs the original gelatin capsule of risedronate in 25 elderly healthy volunteers (12 men and 13 women; mean age, 66 years) suggested that esophageal transit of film-coated tablets is faster than that of gelatin capsules.<sup>26</sup>

Although there is plenty of evidence of antifracture efficacy of alendronate, fracture outcome data are needed for risedronate. Additional insights into the safety of risedronate use in the setting of hepatic impairment or other organ system disease are needed, as is information on long-term safety and efficacy.

## CONCLUSIONS

In postmenopausal women with normal bone density, risedronate, 5 mg/d, increases lumbar spine bone density and preserves femoral neck density. In postmenopausal women with prior vertebral fracture, it decreases new vertebral and nonvertebral fracture incidence. In a study<sup>21</sup> of patients who experienced breast cancer and who have chemotherapy-induced menopause, risedronate, with or without tamoxifen, preserved trabecular and cortical bone. Risedronate prevented corticosteroid-induced vertebral bone loss in a study<sup>22</sup> of men and women beginning long-term corticosteroid therapy.

Clinical studies<sup>12,15-20</sup> show that cyclical risedronate, 30 mg/d, for 28 to 84 days safely decreases pagetic bone pain and induces normaliza-

tion of the alkaline phosphatase level in most subjects with Paget disease, in addition to inducing radiological improvement in pagetic lesions, without causing deleterious bone effects. It may turn out to be more effective than etidronate because of a shorter required duration of therapy, higher rates of and longer-lasting remission, and significant pain reduction in patients who have not adequately responded to etidronate in the past.

The safety data from all of the randomized controlled trials in settings of postmenopausal osteoporosis, breast cancer, corticosteroid use, and Paget disease suggest that the adverse effect profile of risedronate is similar to that of placebo. Risedronate, one of the most potent known bisphosphonates, does not appear to interfere with bone mineralization in doses used clinically for osteoporosis or Paget disease and is thus unlikely to increase long-term fracture risk. However, long-term toxic effects and efficacy data, particularly fracture end point data, are lacking at this time. Also unknown are the optimal duration of therapy, the potential for use in combination with other agents, and whether risedronate may hold any clinical advantage over alendronate.

Since the submission of the manuscript, 5 randomized controlled trials<sup>38-42</sup> pertinent to risedronate in osteoporosis have been published. Two of the trials<sup>41,42</sup> show that regardless of the number of years since menopause, risedronate, 5 mg/d given for 2 to 3 years, increased spine and hip bone density and decreased the risk of new vertebral fractures by 50%<sup>42</sup> in postmenopausal women with low bone density at baseline. Two other trials<sup>38,40</sup> reported that risedronate, 5 mg/d for 12 months, increased lumbar and hip density in men and women chronically taking prednisone long-term ( $\geq 7.5$  mg/d or the equivalent) and decreased vertebral fracture risk by 70%.<sup>38</sup> Risedronate at a lower 2.5-mg/d dose or at 15 mg/d for 2 of each 12 weeks preserved lumbar and hip bone mass in postmenopausal women taking 2.5 mg or more of prednisone daily for rheumatoid arthritis.<sup>39</sup> All trials determined gastrointestinal adverse events of risedronate to be similar to those of placebo.

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## REFERENCES

1. Risedronic acid: NE 58095, risedronate sodium, Actonel. *Drugs R D*. 1999;1:218-220.
2. Risedronate for Paget's disease of bone. *Med Lett Drugs Ther*. 1998;40:87-88.
3. Watts NB. Treatment of osteoporosis with bisphosphonates. *Rheum Dis Clin North Am*. 1994;20:717-734.
4. Russell RG, Rogers MJ. Bisphosphonates: from the laboratory to the clinic and back again. *Bone*. 1999;25:97-106.
5. Watts NB. Treatment of osteoporosis with bisphosphonates. *Endocrinol Metab Clin North Am*. 1998;27:419-439.
6. Reginster JY. Treatment of bone in elderly subjects: calcium, vitamin D, fluor, bisphosphonates, calcitonin. *Horm Res*. 1995;43:83-88.
7. Gatti D, Adami S. New bisphosphonates in the treatment of bone diseases. *Drugs Aging*. 1999;15:285-296.
8. Goa KL, Balfour JA. Risedronate. *Drugs Aging*. 1998;13:83-91; discussion, 92.
9. Hodsmen A, Adachi J, Olszynski W. Prevention and management of osteoporosis: consensus statements from the Scientific Advisory Board of the Osteoporosis Society of Canada, 6: use of bisphosphonates in the treatment of osteoporosis. *CMAJ*. 1996;155:945-948.
10. Boyce RW, Wronski TJ, Ebert DC, et al. Direct stereological estimation of three-dimensional connectivity in rat vertebrae: effect of estrogen, etidronate and risedronate following ovariectomy. *Bone*. 1995;16:209-213.
11. Harris ST, Watts NB, Genant HK, et al, for the Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. *JAMA*. 1999;282:1344-1352.
12. Miller PD, Brown JP, Siris ES, Hoseyni MS, Axelrod DW, Bekker PJ, for the Paget's Risedronate/Etidronate Study Group. A randomized, double-blind comparison of risedronate and etidronate in the treatment of Paget's disease of bone. *Am J Med*. 1999;106:513-520.
13. Clemmesen B, Ravn P, Zegels B, Taquet AN, Christiansen C, Reginster JY. A 2-year phase II study with 1-year of follow-up of risedronate (NE-58095) in postmenopausal osteoporosis. *Osteoporos Int*. 1997;7:488-495.
14. Mortensen L, Charles P, Bekker PJ, Digennaro J, Johnston CC Jr. Risedronate increases bone mass in an early postmenopausal population: two years of treatment plus one year of follow-up. *J Clin Endocrinol Metab*. 1998;83:396-402.
15. Brown JP, Kylstra JW, Bekker PJ, et al. Risedro-

- nate in Paget's disease: preliminary results of a multicenter study. *Semin Arthritis Rheum*. 1994; 23:272.
16. Brown JP, Chines AA, Myers WR, Eusebio RA, Ritter-Hrncirik C, Hayes CW. Improvement of pagetic bone lesions with risedronate treatment: a radiologic study. *Bone*. 2000;26:263-267.
  17. Brown JP, Hosking DJ, Ste-Marie L, et al. Risedronate, a highly effective, short-term oral treatment for Paget's disease: a dose-response study. *Calcif Tissue Int*. 1999;64:93-99.
  18. Siris ES, Chines AA, Altman RD, et al. Risedronate in the treatment of Paget's disease of bone: an open label, multicenter study. *J Bone Miner Res*. 1998;13:1032-1038.
  19. Singer FR, Clemens TL, Eusebio RA, Bekker PJ. Risedronate, a highly effective oral agent in the treatment of patients with severe Paget's disease. *J Clin Endocrinol Metab*. 1998;83:1906-1910.
  20. Hosking DJ, Eusebio RA, Chines AA. Paget's disease of bone: reduction of disease activity with oral risedronate. *Bone*. 1998;22:51-55.
  21. Delmas PD, Balena R, Confravreux E, Hardouin C, Hardy P, Bremond A. Bisphosphonate risedronate prevents bone loss in women with artificial menopause due to chemotherapy of breast cancer: a double-blind, placebo-controlled study. *J Clin Oncol*. 1997;15:955-962.
  22. Cohen S, Levy RM, Keller M, et al. Risedronate therapy prevents corticosteroid-induced bone loss: a twelve-month, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Arthritis Rheum*. 1999;42:2309-2318.
  23. Mitchell DY, Heise MA, Pallone KA, et al. The effect of dosing regimen on the pharmacokinetics of risedronate. *Br J Clin Pharmacol*. 1999;48:536-542.
  24. Mitchell DY, Eusebio RA, Dunlap LE, et al. Risedronate gastrointestinal absorption is independent of site and rate of administration. *Pharm Res*. 1998;15:228-232.
  25. Mitchell DY, Eusebio RA, Sacco-Gibson NA, et al. Dose-proportional pharmacokinetics of risedronate on single-dose oral administration to healthy volunteers. *J Clin Pharmacol*. 2000;40:258-265.
  26. Perkins AC, Wilson CG, Frier M, et al. Esophageal transit of risedronate cellulose-coated tablet and gelatin capsule formulations. *Int J Pharm*. 1999;186:169-175.
  27. Patel S, Pearson D, Bhalla A, Maslanka W, White DA, Hosking DJ. Changes in bone mineral density in patients with Paget's disease treated with risedronate. *Ann Rheum Dis*. 1997;56:405-409.
  28. *Physicians' Desk Reference: PDR*. Oradell, NJ: Medical Economics Co; 2000:v.
  29. Tanahashi M, Funaba Y, Tateishi A, Kawabe N, Nakadate-Matsushita T. TRK-530 inhibits accumulation of superoxide anions derived from human polymorphonuclear leukocytes and bone resorption induced by activated osteoclasts. *Pharmacology*. 1998;56:125-130.
  30. Bone HG, Greenspan SL, McKeever C, et al, for the Alendronate/Estrogen Study Group. Alendronate and estrogen effects in postmenopausal women with low bone mineral density. *J Clin Endocrinol Metab*. 2000;85:720-726.
  31. Patel S. Current and potential future drug treatments for osteoporosis. *Ann Rheum Dis*. 1996; 55:700-714.
  32. Boyce RW, Paddock CL, Franks AF, Jankowsky ML, Eriksen EF. Effects of intermittent hPTH(1-34) alone and in combination with 1,25(OH)(2) D(3) or risedronate on endosteal bone remodeling in canine cancellous and cortical bone. *J Bone Miner Res*. 1996;11:600-613.
  33. Ejersted C, Oxlund H, Andreassen TT. Bisphosphonate maintains parathyroid hormone (1-34)-induced cortical bone mass and mechanical strength in old rats. *Calcif Tissue Int*. 1998;62: 316-322.
  34. Jee WS, Lin BY, Ma YF, Ke HZ. Extra cancellous bone induced by combined prostaglandin E2 and risedronate administration is maintained after their withdrawal in older female rats. *J Bone Miner Res*. 1995;10:963-970.
  35. Ma YF, Pan Z, Jee WS, et al. Intermittent on/off prostaglandin E2 and risedronate are equally anabolic as daily PGE2 alone treatment in cortical bone of ovariectomized rats. *J Bone Miner Res*. 1997; 12:2108-2112.
  36. Boissier S, Magnetto S, Frappart L, et al. Bisphosphonates inhibit prostate and breast carcinoma cell adhesion to unmineralized and mineralized bone extracellular matrices. *Cancer Res*. 1997; 57:3890-3894.
  37. Sasaki A, Boyce BF, Story B, et al. Bisphosphonate risedronate reduces metastatic human breast cancer burden in bone in nude mice. *Cancer Res*. 1995;55:3551-3557.
  38. Wallach S, Cohen S, Reid DM, et al. Effects of risedronate treatment on bone density and vertebral fracture in patients on corticosteroid therapy. *Calcif Tissue Int*. 2000;67:277-285.
  39. Eastell R, Devogelaer JP, Peel NF, et al. Prevention of bone loss with risedronate in glucocorticoid-treated rheumatoid arthritis patients. *Osteoporos Int*. 2000;11:331-337.
  40. Reid DM, Hughes RA, Laan RF, et al. Efficacy and safety of daily risedronate in the treatment of corticosteroid-induced osteoporosis in men and women: a randomized trial: European Corticosteroid-Induced Osteoporosis Treatment Study. *J Bone Miner Res*. 2000;15:1006-1013.
  41. Fogelman I, Ribot C, Smith R, Ethgen D, Sod E, Reginster JY, for the BMD-MN Study Group. 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.
  42. Reginster J, Minne HW, Sorensen OH, et al, for the Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. *Osteoporos Int*. 2000;11:83-91.