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EXPERT REVIEW

Risedronate's Role in Reducing Hip Fracture in Postmenopausal Women with Established Osteoporosis

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Abstract: Osteoporosis is a significant concern for postmenopausal women and is a critical factor in hip fracture. Examining evidence for osteoporosis medications in hip fracture is important for optimizing treatment**.**
Purpose: Review risedronate's role for hip fracture in postmenopausal women.
Methods: A literature search was conducted using Medline and Web of Science. The search was limited using the terms "risedronate" and "hip fracture," and to studies that included women. Similar articles linked to the search and pertinent articles in bibliographies were also examined.
Results: Risedronate has demonstrated efficacy and cost effectiveness for hip fracture, but may not be beneficial for patients with low fracture risk. Risedronate is generally well tolerated, but may cause side effects in some patient populations.
Conclusion: Risedronate has benefit for hip fracture, but patients should be carefully screened to determine the appropriateness of risedronate before starting treatment.

Keywords: risedronate, hip fracture, osteoporosis, bisphosphonate, postmenopausal women

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Introduction

Osteoporotic fractures are a common problem, with an estimated 9 million that occurred worldwide in 2000.[1] Among these, hip fractures have received substantial attention because of their potential effect on quality of life. There were 1.66 million hip fractures worldwide in 1990, but it has been estimated that 6.26 million fractures will occur annually worldwide by 2050 assuming the rate of hip fracture does not decline.[2] Interestingly, research has indicated that non-hip fractures contribute to greater morbidity than hip fractures up to the age of 75.[3] Hip fractures are important because they have been associated with mortality, but the direct impact on mortality has been difficult to quantify because of the high rate of co-morbidities in patients who experience hip fractures.[4,5] Together, these data indicate that hip fractures become an increasingly important health concern as people age and develop a greater number of co-morbidities. Postmenopausal women represent a group at high risk for osteoporosis, and the rise in hip fracture burden with increasing age was supported by a study in Australia in postmenopausal women that estimated the 5-year risk of hip fracture.[6] This analysis utilized a Markov process with Monte Carlo simulations and found that the risk of hip fracture increased substantially for the oldest patients. For instance, patients aged 75–79 had a 5-year risk for first hip fracture of 3.8%, while those aged 90 and older had a 20.9% risk. Hip fracture clearly presents a problem for aging, and evaluating medications to weigh their benefit and potential risk in older women with greater co-morbidities is therefore important.

Bisphosphonates have become a mainstay in treating and preventing osteoporosis, and studies with these agents have shown that they are more effective at reducing vertebral fractures than hip fractures. For example, in the pivotal BONE trial for ibandronate, there was not a statistically significant benefit for non vertebral fracture.[7] However, even the bisphosphonates which have shown significant benefit for hip fracture require a larger number needed to treat (NNT) to prevent one hip fracture than is necessary to prevent one vertebral fracture. Therefore, a closer examination of the data for bisphosphonates specific to hip fracture is important to better characterize which patients will receive benefit from these medications. This article focuses on risedronate, which has received interest because its cyclical side chain (compared to alendronate's amino side chain) may improve its gastrointestinal tolerability. Studies reviewed include those assessing risedronate's impact and cost for hip fracture in post menopausal women as well as those examining available safety data.

Mechanism of Action

Risedronate is classified as a nitrogen-containing bisphosphonate. Bisphosphonates exert their effect by inhibiting bone resorption that normally occurs in the body during the bone remodeling process. Part of this effect is exerted through binding to hydroxyapatite crystals within bone matrices, which prevents both calcification and breakdown of hydroxyapatite and in turn reduces bone resorption.[8,9] In addition, osteoclasts, the cells responsible for breaking down bone during the remodeling process, also ingest bisphosphonates through endocytosis. Once inside the osteoclast, nitrogen-containing bisphosphonates such as risedronate interfere with the intracellular mevalonate pathway, which in turn inhibits the production of sterols, cholesterols, and lipids.[10,11] Interference with this pathway affects post-translational modification of key cellular proteins, which subsequently alters regulation of osteoclast activity and may result in osteoclast apoptosis.[12]

Pharmacokinetics and Metabolism

Risedronate, like other bisphosphonates, is poorly absorbed from the digestive tract. For instance, the mean bioavailability of the 30 mg tablets is 0.63%.[13] Taking the medication with food can further affect absorption; therefore, the medication is recommended to be administered 30 minutes before breakfast. Risedronate is not metabolized, and any risedronate that is not absorbed from the digestive tract is excreted unchanged in the feces. Approximately 60% of the dose absorbed is adsorbed by the bone, and the remainder is excreted unchanged by the kindey.[13] Steady state is reached by 57 days after starting treatment. In post-menopausal women the half-life was found to be 561 hours.[13]

Clinical Studies

A Cochrane review pooled data from 7 risedronate studies to evaluate its impact on fracture in postmenopausal women.[14] This review found an NNT of 100 to

prevent one hip fracture. However, this analysis also concluded that risedronate may not prevent hip fractures in patients who do not have low bone density or a previous vertebral fracture. Therefore, it is important to examine risedronate's data in different patient groups to evaluate the benefit of risedronate when a patient's risk factors are specifically considered.

For hip fracture, the Cochrane review included data from one small primary prevention trial in which no patients in either group experienced a hip fracture as well as three trials for secondary prevention of hip fracture. Two of the secondary studies were part of the VERT trial, which was published as separate analyses, one from North America and the other from Australia and Europe.[15,16] Both studies used a randomized, double-blind, placebo-controlled design, and patients received 2.5 mg risedronate, 5 mg risedronate, or placebo daily for 3 years. However, the 2.5 mg arm was stopped early because of lack of efficacy in other risedronate studies. Enrollment criteria included being age 85 years or younger and 5 or more years post-menopause, and having either 2 or more radiographically identified vertebral fractures or one vertebral fracture and a T-score ≤−2. Patients were not excluded for a history of gastrointestinal (GI) events but were excluded for recent use of drugs affecting bone metabolism. In the VERT-North America trial, patients were similar with regard to baseline characteristics, which included smoking status, height, and weight.[15] In the international VERT trial patients were also considered to be similar, and height was included as a risk factor.[16] The VERT-North America trial used vertebral fractures as the primary outcome.[15] Non-vertebral fractures were measured, but hip and pelvis fractures were reported together as one outcome, preventing an exact determination of risedronate's impact on hip fracture. Using this combined outcome, 12 patients in the risedronate group and 15 in the placebo group experienced an event. However, statistical significance was not reported. In the international VERT trial, hip fracture was reported separately (11 out of 406 in placebo group vs 9 out of 406 in the risedronate 5 mg group over a 3 year period).[16] However, statistical significance was not provided. In an extension of this study in which 105 women taking placebo and 115 women taking risedronate 5 mg completed the extension, no new hip fractures occurred in either group during the additional 2 years of treatment.[17]

The final secondary prevention trial included in the Cochrane analysis, the largest trial studying risedronate for hip fracture, was the Hip Intervention Program (HIP). HIP focused on postmenopausal women 70 years and older.[18] Patients receiving risedronate were divided into 2 groups. The first group included 70–79 year old women with a T-score <−4.0, or a T-score <−3.0 and at least 1 risk factor for hip fracture; the second group included patients ≥80 years old who met one of the following criteria: ≥1 clinical risk factor for hip fracture, a hip T-score of <−4.0, or a femoral neck T-score of <−3.0 along with a hip axis length of ≥11.1 cm. Patients in the ≥80 years old group were not required to have a bone density available, and the majority were enrolled based on a single clinical risk factor for hip fracture. Patients were excluded for any major medical illness, abnormal lab results, and recent use of medications that affect bone, but they were not excluded for GI issues. Patients were similar at baseline between groups, and other risk factors recorded included height, weight, and serum 25-hydroxyvitamin D levels. Patients were treated for 3 years with 2.5 mg risedronate daily, 5 mg risedronate daily, or placebo. A total of 3624 risedronate patients and 1821 placebo patients were enrolled in the 70–79 group while 2573 risedronate and 1313 placebo patients were enrolled in the ≥80 year group. The average age was 74 for the 70–79 year old group and 83 for the ≥80 year old group, and 98% of the patients were Caucasian. In the final analysis, patients taking the 2.5 mg and 5 mg doses were combined into one group and compared to placebo. In the 70–79 year old group, an absolute risk reduction (ARR) in hip fracture of 1.3% was observed, giving an NNT of 77 ($P = 0.009$). A subanalysis of patients in this group with known vertebral fracture at baseline had an ARR of 3.4% for hip fracture vs. placebo (NNT = 29, $P = 0.003$). In the ≥80 year old group no significant differences were found between risedronate and placebo. However, the study authors noted that there was a potentially low rate of osteoporosis in this group. Since the majority of patients enrolled in this group qualified based on clinical risk factors, it is possible that many patients would not have qualified based on bone density criteria. Data specifically for patients in this group who had a T-score available were not provided.

A post-hoc analysis of the HIP trial combined the 70–79 and ≥80 year old groups but included only those patients who had confirmed osteoporosis, as defined by a baseline femoral neck T-score ≤–2.5 and 1 or more prior vertebral fracture(s).[19] Using these criteria, 1656 women (1090 who received risedronate and 566 who received placebo) from the intent to treat population were included in the analysis. Over the 3 year treatment period, in the placebo group 7.4% of the women experienced a hip fracture compared to 3.8% of the women who took risedronate (ARR 3.6%, NNT = 28, 95% Confidence Interval [CI] 0.32–0.91, $P = 0.019$). Therefore, the data indicates that patient risk plays an important role in whether treatment with risedronate will provide benefit.

In order to further examine the effect of risedronate on the oldest patients who may be candidates for its use, an analysis was conducted that pooled data from the HIP and VERT trials for patients ≥80 years.[20] Pooling this data offered further insight into older patients with higher risk for fracture because the VERT trial required a higher degree of risk for enrolment than patients entering the ≥80 years of age group in the HIP trial. In this combined analysis, 704 patients received treatment with risedronate and 688 received placebo. The mean age for both groups was 83. Though benefit was found for vertebral fractures, there was still no benefit of risedronate on non-vertebral fractures.

Additional studies by Sato and colleagues not included in the Cochrane analysis observed risedronate's impact on hip fracture in specific patient populations in Japan at higher risk for fracture. One study focused on older women after stroke.[21] Patients were at least 65 years of age (mean age 71.6 for placebo and 71.2 for risedronate) and were randomized to either 2.5 mg of risedronate daily or placebo for 1 year. Patients were excluded if they had taken any medications that could affect bone metabolism (including vitamin D) and were also excluded for renal insufficiency, hepatic disease, and cardiac failure. The BMD was taken from metacarpal measurements, was similar between groups, and was within the normal range. Each study group began with 187 patients, and 173 patients in the risedronate group and 172 in the placebo group completed the study. The two groups were considered were similar for demographic information, including baseline measurements of bone turnover. A hip fracture occurred in 7 of the 173 patients in the placebo group and in 1 of the 172 risedronate treated patients, (ARR = 3.4%, NNT = 29 for those completing the study, $P = 0.036$). Though statistical significance was not reported, patients taking placebo experienced greater loss of BMD on the hemiplegic side than on the unaffected side (4.9% compared to 2.4%), compared with a 1.5% gain in BMD on the hemiplegic side in the risedronate group.

In another study by Sato et al., risedronate was given to patients who had been diagnosed with dementia and probable Alzheimer's Disease.[22] Patients were required to be 70 or older and were followed for 18 months. Patients were excluded for a known cause of osteoporosis (such as renal osteodystrophy), as well as for use of a medication affecting bone metabolism for 3 months or longer in the 12 months prior to enrollment. Both the placebo and treatment groups enrolled 250 patients. The two groups were similar at baseline, including factors such as BMI, calcium and vitamin D intake, and falls prior to study entry. All patients were given 1000 IU of ergocalciferol and 1200 mg of elemental calcium daily. The treatment group also received 2.5 mg of risedronate once daily. Patients received treatment and were followed for 18 months. Evaluation of BMD was done by metacarpal measurement. Both groups had lower BMD than the reference for the normal Japanese population, but statistical significance was not provided. In the risedronate group, 231 patients completed the trial compared with 230 in the placebo group. The study utilized an intention-to-treat analysis, and 5 patients in the risedronate group and 19 patients in the placebo group experienced a hip fracture with 18 months of treatment (ARR 5.6%, NNT = 18, $P < 0.001$). Though these trials are small, they provide interesting evidence because of the low NNT with use of 2.5 mg of risedronate, which is generally not considered to be an effective treatment dose.

Though the trials with risedronate discussed above lasted up to 3 years, an analysis of risedronate trials by Harrington et al. found a statistically significant reduction in non-vertebral fractures after 6 months of risedronate treatment. However, because hip fractures were less frequent in the studies than other non-vertebral fractures, such as those of the wrist, a specific analysis of hip fractures was not provided. Therefore, it is difficult to determine if risedronate can

significantly reduce hip fractures with only 6 months of treatment.[23]

Head-to-Head studies

Direct comparisons of the bisphosphonates are of interest to determine which is the most effective. However, there are a limited number of these studies, and those available either are retrospective analyses or compared BMD only rather than fracture rate. A prospective head-to-head study, FACT, compared 1053 postmenopausal women treated for one year with either 70 mg alendronate weekly or 35 mg of risedronate weekly.[24] This study measured BMD changes and changes in bone markers. Significantly more patients treated with alendronate than risedronate achieved gains in BMD at various sites while significantly more risedronate patients experienced bone loss at those same sites. However, comparisons between agents can be difficult based only on BMD and bone turnover markers. For example, an analysis examined the correlation between bone density and non-vertebral fracture using a COX regression model and data from both VERT studies and the HIP trial.[25] This analysis found that changes in lumbar BMD explained only 12% of risedronate's effect on non-vertebral fracture risk (95% CI 2%, 21%, $P = 0.014$), and changes in femoral neck BMD explained only 7% of the effect on non-vertebral fracture risk (95% CI 2%, 13%, $P = 0.005$). Therefore, differences in BMD may not necessarily indicate a change in fracture risk.

Retrospective analyses have also been completed to attempt to compare fracture rates based on use in clinical practice. A retrospective study of 41,135 records from Medicare beneficiaries compared the fracture rates associated with various osteoporosis treatments after one year of treatment.[26] This analysis found no difference in hip fracture rate between alendronate and risedronate for up to 2 years after treatment initiation (hazard ratio for taking risedronate 0.92, 95% CI 0.70 to 1.20).

Another retrospective analysis, REAL, compared data from 21,615 women aged 65 and over taking once-weekly alendronate and 12,215 taking once-weekly risedronate.[27] Risedronate had a significantly lower risk of hip fractures, but to prevent one additional hip fracture taking risedronate compared to alendronate, the NNT was 476 ($P = 0.01$). A potentially complicating factor is that alendronate 35 mg weekly, which is used for prevention, and 70 mg weekly, which is used for treatment, were combined into one group and compared directly with 35 mg of risedronate weekly, which is used for both prevention and treatment.

The retrospective REALITY analysis also used a large healthcare database to compare the effects of alendronate and risedronate on fractures.[28] The analysis included women 65 years and older and utilized records of 12,956 patients taking treatment doses of alendronate and 6107 taking treatment doses of risedronate. Statistics were performed using a Cox proportional hazards model. This analysis found that patients taking risedronate had approximately one additional fracture for every 200 patient years of treatment compared to alendronate (relative risk [RR] 1.77, 1.15–2.74, $P = 0.01$), even though the overall fracture risk was similar between the two groups. A complicating factor that will be discussed later in the paper is that full records could not be completed for the majority of patients because of poor medication adherence.

Jansen et al., conducted a Bayesian network meta-analysis of the bisphosphonates to determine the probability that one of the bisphosphonates would be more effective in preventing fracture.[29] This analysis concluded that ibandronate had a 47% probability of having the greatest reduction in fracture risk, while alendronate had a 36% probability and risedronate had an 11% probability of having the lowest risk. This analysis looked at all fractures; therefore, it is difficult to directly determine a comparative effect on hip fracture, especially considering that ibandronate's effect on hip fracture in the BONE trial did not reach statistical significance.

A meta-analysis by Liberman et al., comparing different treatments for osteoporosis concluded that alendronate may be more effective than other osteoporosis treatments for reducing fractures.[30] However, the meta-analysis compared relative risk reduction among the agents. With the different initial designs for various trials, it can be difficult to make decisions based on relative risk. For instance, this meta-analysis found the relative risk reduction (RRR) for hip fracture was 55% when taking alendronate compared to placebo, while the RRR was 26% when taking risedronate. This RRR for alendronate matched the RRR for hip fracture found in the FIT trial, which

was one of the largest studies involving alendronate. The FIT trial had an ARR of 1.1% for hip fracture, giving an NNT of 90. For comparison, the Cochrane review of risedronate for hip fracture found an NNT of 100, and the NNT was 77 for the 70–79 year old group in the HIP trial with risedronate. Therefore, comparisons across trials must be made carefully, and RRR alone may not be a reliable barometer to use for comparison.

A systematic review of trials with osteoporosis treatments found that that there was good evidence that alendronate, risedronate, and estrogen are more likely than placebo to prevent hip fractures and that there is fair evidence that zoledronic acid prevents hip fracture more than placebo.[31] However, the study authors also concluded that there is insufficient evidence to determine the relative efficacy and safety of the treatments.[31]

Cost effectiveness for hip fracture

With the varying NNT found for patients at different risk levels for fracture, evaluating risk before initiating treatment may help to avoid unnecessary medical costs. For instance, in the HIP study's 70–79 year old group without a vertebral fracture, the NNT of 77 for 3 years indicates that 231 patient years of treatment would be required to prevent one hip fracture. In contrast, the HIP study's 70–79 group with a previous vertebral fracture would have a substantially smaller cost with an NNT of 29, giving 87 patient years of treatment to prevent one fracture. Currently, risedronate costs over $1200.00 per year in the United States. Therefore, preventing one hip fracture could be very expensive depending on the medication costs in a given country. However, the cost of treating a hip fracture and the impact of fracture on the patient's quality of life must also be considered in a cost-effectiveness analysis, and some studies have provided a deeper analysis into the cost effectiveness of risedronate for hip fracture.

An analysis using a Markov model evaluated the cost of osteoporosis treatments for fracture for patients in Germany.[32] This model assumed 3 years of treatment with medication and calculated the cost to prevent fracture over a 10 year time period. Risedronate and alendronate were the only medications with sufficient data to be included in the analysis for hip fracture, and this study determined that preventing one hip fracture with risedronate cost 37,348 euro compared to 48,349 euro for alendronate. The cost per quality adjusted life year (QALY) gained with risedronate was 32,092 euro while for alendronate the cost per QALY was 41,302 euro. The costs calculated in this analysis were based on 2004 data, and the current availability of generic alendronate could alter this comparison. However, analyses based on costs in Canada and Italy using efficacy data from the REAL study found brand-name risedronate to be more cost effective than generic alendronate.[33,34] These studies also included other fracture types in the costs analysis; therefore, an exact comparison of hip fracture cost cannot be extrapolated. In addition, use of a different study as the basis for efficacy, such as the REALITY study that found greater efficacy for alendronate for hip fracture,[28] could give a different cost effectiveness outcome.

A recent cost-effective analysis compared denosumab to risedronate and alendronate in postmenopausal women ≥60 years meeting criteria for osteoporosis in Belgium.[35] This analysis concluded that denosumab was more cost effective than both branded risedronate and generic alendronate. However, this model assumed a 46% lower discontinuation rate in denosumab patients compared to bisphosphonates that would need verification in practice to ensure that patients visited their provider in a timely manner to have this administered. This model also included data for vertebral, hip, and other nonvertebral fractures, making a direct comparison of hip fracture cost effectiveness difficult.

One study provided guidance for initiating treatment by calculating the 10-year hip fracture risk threshold that would be necessary for bisphosphonate use to be cost effective for hip fracture in the United States.[36] This analysis utilized a Markov-cohort model with 2005 healthcare costs and assumed an annual bisphosphonate cost of $600.00 (US). Cost-effectiveness was set at $60,000 per quality adjusted life year gained. Using these criteria, bisphosphonate treatment was effective when the 10-year hip fracture risk was 3% or higher. Since this analysis was done specifically for the United States, the cost-effective threshold could vary depending upon actual costs of risedronate and medical treatment in other countries. Even within the United States, the current cost of risedronate is approximately twice the

estimated cost in this example and clinical judgment is therefore needed.

The 10-year fracture risk threshold was calculated in this study because it was designed to be used with the World Health Organization (WHO)'s FRAX tool. The FRAX tool was developed to help clinicians better determine absolute fracture risk.[37] FRAX calculates the 10-year fracture risk for both a major osteoporotic fracture and a hip fracture based on data from 12 questions and a BMD test if it is available. Clinical judgment is still necessary because of the variability of some factors. For instance, a female patient who is 80 years old, has a normal BMI, has no clinical risk factors, but does not have a BMD available is considered to have a 10-year fracture risk above the 3% cost effectiveness threshold and therefore would be recommended for treatment. However, data from the HIP trial (whose patients had to have at least one clinical risk factor to be entered rather than no factors like this sample patient) indicates that the sample patient would not receive benefit from risedronate. However, if a normal BMD is also included in the FRAX analysis, the patient no longer meets the cost effectiveness threshold. Therefore, a BMD is important in determining if treatment would be cost effective. Another consideration for FRAX is whether the patient's expected lifespan may be shorter than the 10-year time horizon. If other medical conditions may shorten the patient's lifespan, the likelihood of fracture determined by FRAX can be adjusted proportionately. For instance, if FRAX determined a patient had a 10% likelihood of hip fracture, the one year risk would be one-tenth of this value, or 1%.[37] The FRAX tool is available online at http://www.shef.ac.uk/FRAX/ and is also available as paper charts that can be downloaded from the site.

Risedronate Safety

The Cochrane Review studying risedronate for hip fracture determined that there is imprecise information available to make judgments regarding the risk of adverse effects from risedronate, especially for rare side effects such as osteonecrosis of the jaw.[14] However, the Cochrane review was completed based on trials to assess efficacy rather than safety, and further study has been done to assess specific side effects.

Upper GI tract safety

A pooled analysis of upper GI tract safety of risedronate 5 mg daily did not show a difference compared to placebo even among patients with a higher risk of such events.[38] This analysis included 9 multicenter, double-blind, randomized, placebo-controlled trials conducted between November 1993 through April 1998 with 5020 subjects who received risedronate 5 mg compared to 5048 patients who took placebo. At study entry, many subjects had a history of gastrointestinal problems in each group (61.1% of placebo and 61.0% of risedronate patients). The two groups were similar for history of GI disease, active GI tract disease, use of antisecretory drugs during the studies, and use of aspirin or NSAIDS during the studies. Following risedronate treatment, the upper GI tract adverse event rate was 29.6% in the placebo group compared with 29.8% in the risedronate group, and the upper GI tract event rate per 100 patient years was 19.2 in the placebo group versus 20 in the risedronate group ($P = 0.3$). Patients on risedronate 5 mg daily did not experience worsening of their existing active heartburn, esophagitis, other esophageal disorders, or peptic ulcer disease. Endoscopy performed in 349 subjects did not show statistical difference between the groups.[38]

A small study looked at the tolerability of risedronate specifically for patients who previously had been unable to tolerate alendronate due to upper gastrointestinal events.[39] Sixty-six post-menopausal women were enrolled, with 35 receiving risedronate 5 mg daily and 31 receiving placebo. In the placebo group, 5 patients stopped treatment because of gastrointestinal complaints compared with 4 patients from the risedronate group (95% CI -29.6% to 17%). The number of patients who continued to take treatment and experienced adverse gastrointestinal events (19.4% placebo, 20.0% risedronate) was considered comparable between the groups (95% CI not provided).

Atypical fracture risk

A US Food and Drug Administration (FDA) Drug safety communication on October 13, 2010 identified the risk of atypical fractures of the thigh, known as subtrochanteric and diaphyseal femur fractures, in patients who take bisphosphonates for osteoporosis.[40] Diaphyseal femur fractures occur in the long part of the thigh bone. These fractures are very uncommon

and appear to account for less than 1% of all hip and femur fractures in the general population. It is not clear if bisphosphonates are the cause in patients using these medications.[40] According to the Atypical Femoral Fracture Task Force Report, the majority (120 of 169) such cases occurred after oral alendronate monotherapy, and 12 patients were treated with oral risedronate (of these, one patient received risedronate followed by oral alendronate, 2 were treated with alendronate prior to risedronate, and another was treated with etidronate prior to risdedronate).[41] Median duration of bisphosphonate treatment was 7 years. The task force report concluded that the incidence of atypical fractures associated with bisphosphonate therapy for osteoporosis appears to be very low, particularly compared with the number of vertebral, hip, and other fractures that are prevented by bisphosphonates. Moreover, a causal association between bisphosphonates and atypical fractures has not been established. However, recent observations suggest that the risk rises with increasing duration of exposure, and there is concern that lack of awareness and underreporting may mask the true incidence of the problem.[41] Given the relative rarity of atypical femoral fractures, the task force recommends that specific diagnostic and procedural codes be created and that an international registry be established to facilitate studies of the clinical and genetic risk factors as well as optimal surgical and medical management of these fractures.[41]

Atrial fibrillation

The development of atrial fibrillation following treatment also has been a concern for the bisphosphonates. A pooled analysis of risedronate phase 3 placebo controlled clinical trials evaluated non-adjudicated adverse events of atrial fibrillation, cerebrovascular accidents, and death from these events in approximately 15,000 patients who received treatment for about 2 years.[42] There was no significant difference in the incidence of atrial fibrillation, cerebrovascular accidents, and death from these events between risedronate and placebo. However, it may be reasonable to use risedronate cautiously in patients who already have atrial fibrillation or other cardiac issues.

Renal toxicity

The US product label states that risedronate not be given to patients with severe renal dysfunction defined as creatinine clearance (CrCl) of <30 mL/min, due to lack of prospective efficacy and safety data in this population.[13] A pooled retrospective analysis included 9 double-blind, randomized, placebo-controlled phase III studies in patients who received risedronate 5 mg or placebo for an average exposure of 2 years duration. Adverse events related to renal function were similar between the risedronate and placebo groups in all renal impairment subgroups: mild ($\text{CrCl} \geq 50$ and <80 mL/min), moderate ($\text{CrCl} \geq 30$ and <50 mL/min) and severe ($\text{CrCl} < 30$ mL/min).[43]

Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) has been linked to high-dose intravenous bisphosphonate use in bone cancers, but ONJ has also been observed at a much lower incidence in patients on oral bisphosphonates taken for osteoporosis.[44] According to the American Dental Association Expert Panel opinion, the risk of ONJ with bisphosphonate therapy is very low, with approximately 0.7 per 100,000 person-years exposure to alendronate. Other nitrogen-containing oral bisphosphonates, such as risedronate, are expected to have similar risk.[45] The US prescribing information for risedronate states that discontinuation of the medication for patients requiring invasive dental procedures may reduce the risk of ONJ.[13] The American Association of Maxillofacial Surgeons has published a position paper that provides further guidance for bisphosphonates regarding dental procedures.[46] For individuals who have taken an oral bisphosphonate for less than three years and have no clinical risk factors, no alteration or delay in the planned surgery is recommended. For those patients who have taken an oral bisphosphonate for more than three years with or without any concomitant prednisone or other steroid medication, the prescribing provider should be contacted to consider discontinuation of the oral bisphosphonate for three months prior to oral surgery. If possible, the bisphosphonate should not be restarted until osseous healing has occurred.

Cancer risk

There has been concern regarding possible risk of esophageal cancer with bisphosphonates. The largest review of this to date utilized the UK General Practice Research Database to compare cancer rates in patients taking bisphosphonates with nonusers.[47]

In each group 41,826 records were included. In the bisphosphonate group 37 gastric cancers and 79 esophageal cancers occurred compared with 43 gastric cancers and 72 esophageal cancers in the nonuser group, which was not significantly different (adjusted hazard ratio for combined outcome 0.96 [95% CI, 0.74–1.25]). Esophageal cancers alone also did not reach statistical significance (adjusted hazard ratio, 1.07 [95% CI, 0.77–1.49]). Therefore, cancer risk alone does not appear to be a reason to withhold bisphosphonate treatment, but more data is needed for patients who have a previous history of gastric or other cancers.

Musculoskeletal pain

Concern has also been raised regarding musculoskeletal pain caused by the bisphosphonates. A recent retrospective analysis of 26,545 US veterans age 65 and older found no significant relationship between bisphosphonate use and the development of musculoskeletal pain.[48] Data from the original clinical trials of the medications (not head-to-head studies of agents) indicates that use of IV forms of bisphosphonates may be more likely to cause this issue.[49] However, because this issue could present with similar symptoms to other conditions, it is important to consider in a patient taking risedronate and other bisphosphonates.

Ocular inflammation

Though rare, ocular inflammation has been reported in patients receiving bisphosphonates. A case report in a patient treated with alendronate for 6 months then switched to risedronate for 2 months reported bilateral anterior uveitis. It resolved after discontinuation of risedronate.[50] A review of a large VA database did not show a higher rate of uveitis/scleritis in patients treated with bisphophonsphonates (RR 1.23, 95% CI 0.85–1.79).[51]

Dermatologic

Cutaneous adverse events associated with risedronate are reported to be rash (1–10 per 1000)/uncommon, pruritis (1–10 per 10,000)/rare and urticaria/angioedema/bullous reactions/photosensitivity (<1 to 10 per 10,000)/very rare.[52]

Hepatitis

A case report has been published in an 81-year-old woman who developed hepatitis after long term (about 4 years) treatment with risedronate.[53] Patient was receiving metoprolol, fluvastatin, acetaminophen, aspirin and calcium carbonate. Risedronate was discontinued and complete liver function was restored in about 12 months. Bisphosphonate hepatotoxicity is rare but was previously reported with alendronate.[54] The underlying mechanism is unknown.

The US FDA requires medication guides to be issued with all approved prescribed bisphosphonate drugs in US. The medication guide includes information for patients taking bisphosphonates and identifies serious side effects associated with bisphosphonates. These include esophagus problems, low calcium levels, severe jaw bone problems (osteonecrosis), bone joint or muscle pain, and unusual thigh bone fractures.[55] Therefore, the US FDA considers the adverse events from these medications to be similar, and it is difficult to differentiate if one bisphosphonate is less likely to cause these issues. The only potential exception is the possible greater gastrointestinal tolerability that risedronate may possess compared to alendronate.

Patient Preference

Though the major studies with risedronate were completed using a dose of 5 mg daily, patients and prescribers do have other options, as risedronate is also available in a once weekly 35 mg dose, a twice per month dose of 75 mg (given on consecutive days for a total of 150 mg per month) and a single once-monthly dose of 150 mg. Less frequent administration may be beneficial for some patients, and studies provide limited data comparing these different risedronate dosage forms. Other studies also provide insight into medication adherence, which is often thought to be a benefit to the less frequently administered dosage forms.

Only once-daily risedronate has been studied for its ability to reduce fracture, but once-weekly risedronate in doses of both 35 mg and 50 mg were compared in a non-inferiority study with 5 mg risedronate daily based upon effects on lumbar spine BMD.[56] This study lasted one year and enrolled 1456 post-menopausal women 50 years and older. No significant difference was found between the groups, and 35 mg was considered to be the optimal once-weekly dose since there was no greater benefit with 50 mg weekly.

Once-monthly risedronate was compared to once-daily risedronate in a randomized, double-blind, active-controlled, phase II study.[57] This was designed

primarily to evaluate comparative tolerability between doses but evaluated efficacy using BMD and bone turnover markers as a secondary endpoint. All patients were women aged 50 to 85 years who were 5 or more years post-menopausal and had a T-score <–2.0. The daily risedronate dose was 5 mg, and patients taking risedronate once monthly were given doses of 100, 150, or 200 mg for a total of 6 months. A total of 370 patients were enrolled. The 150 and 200 mg monthly doses were not significantly different from the 5 mg daily dose for either BMD or markers of bone turnover, and all of the doses had similar tolerability to the 5 mg daily dose.

Dosage forms that require less frequent administration may be preferable for patients because of reduced pill burden which potentially could result in improved medication adherence. Measures to improve adherence may be particularly important for bisphosphonates because some data indicates that patient adherence with bisphosphonates is poor. In the retrospective REALITY study discussed previously, investigators stopped follow-up if patients were found to be non-adherent with the medication (defined as more than a 15-day gap between fills).[28] Using this criteria, only 22% of the original cohort could still be followed at 1 year after bisphosphonate initiation, and only 3% could be followed after 3 years of treatment.

Studies have also examined the potential impact of a lack of adherence. One study enrolled women aged 60–78 who continued bisphosphonates for at least 2 years.[58] Patient data was obtained from a large administrative database, and the records of 9,063 women were included. The majority were taking alendronate, but 2089 were taking risedronate. For women who stopped the medication, the hazard ratio for a hip fracture at 90 days after stopping bisphosphonate treatment was 1.2 ($P = 0.016$). However, investigators also measured the medication possession ratio (MPR), which is a measure of medication adherence based on the percentage of medication refilled on time. In the subgroup of patients whose MPR was ≥80% for 2 years or longer prior to stopping the bisphosphonate, there was no significant difference in the incidence of hip fracture for up to 9 months after stopping treatment. Another retrospective study evaluated the relationship between fracture risk and adherence for patients taking either risedronate or alendronate.[59] This analysis used a nested case control design with information from a large database in Quebec. Patients were included if taking alendronate at either 10 mg daily or 70 mg weekly or risedronate at either 5 mg daily or 35 mg weekly. Patients were considered to be adherent for taking 80% or more of the medication. Patients whose adherence was <80% had an adjusted RR for hip fracture of 1.28 (95% CI 1.02, 1.61).

Studies have also examined whether the different administration intervals could actually improve adherence. A small study that compared risedronate 5 mg daily and 35 mg weekly found that the weekly regimen actually may be more difficult for some patients to remember.[60] In addition to the risedronate groups, this study also included a placebo group, and 41 patients enrolled in each of the 3 groups. In both the placebo and risedronate 5 mg group, 2 patients were not adherent, but 4 patients were not adherent in the 35 mg weekly group. Though this was a proportionately large increase in nonadherence, it did not reach statistical significance. However, patients in the study reported difficulty with remembering the weekly dose. Therefore, patients and prescribers may need to discuss if daily or weekly administration will be the easiest for a particular patient since available evidence shows the two forms will produce an equivalent effect on bone density when taken as scheduled.

A retrospective analysis of adherence for patients taking ibandronate once monthly compared with those taking alendronate or risedronate once weekly was conducted in France using a large medical database.[61] Patients were over 45 years of age, and the analysis included 1,001 patients in the once-monthly ibandronate group and 1,989 in the once-weekly group (581 taking alendronate and 1408 taking risedronate). A Kaplan-Meier analysis found that patients in the once-monthly group were significantly more likely to be persistent in taking the medication over time ($P < 0.001$). However, the rate of adherence was still low in both groups. The unadjusted persistence rates at 6 months were 57.3% in the once monthly group and 45.7% in the once weekly group, and at 12 months the persistence rates were 47.5% in the monthly group and 30.4% in the weekly group.

Place in Therapy

Various international guidelines recommend a wide range of options as potential first-line treatments for osteoporosis, and a summary of key points

from international guidance published since 2008 is provided in the table.[62–68] However, the guidelines recommend treatments based on both vertebral and non-vertebral efficacy, and not all agents have benefit for hip fracture. Some guidelines do make note of those medications with documented benefit for hip fracture, and these agents include alendronate, denosumab, risedronate, strontium, and zoledronic acid.[63–67] Hormone replacement therapy is also considered to be effective for hip fracture, but most guidelines recommend its use be limited to post menopausal women who clearly need relief from vasomotor symptoms and that it be given for the shortest duration possible.[63–65] Strontium is not mentioned in all guidelines because it is currently not available in the US and Canada, and guidelines note that hip fracture data for strontium was provided for a subset of the population rather than the whole study population.[63,66] Denosumab was not available when some of the guidelines were published and therefore is not mentioned in all guidelines.

A primary reason that multiple agents are considered to be first line is that there are a limited number of

Table 1. Summary of guidance for osteoporosis treatments

Osteoporosis guidelines/guidance	Brief summary of medication recommendations
Author: Raef, et al[62] Organization: King Faisal Specialist Hospital Osteoporosis Working Group Year Published: 2011	Bisphosphonates are first line and alendronate is preferred bisphosphonate; raloxifene and strontium ranelate are second-line agents; teriparatide may be used second-line for some patients; calcitonin should only be used if other agents cannot be.
Author: Body, et al[63] Organization: Belgian Bone Club Year Published: 2010	Bisphosphonates, SERMs, denosumab, and strontium are all potential first-line treatments; states there is insufficient evidence to compare bisphosphonates; hormone replacement should only be used for women with menopause-related symptoms and for the shortest duration possible; teriparatide should be reserved for high-risk patients.
Author: North American Menopause Society[64] Organization: North American Menopause Society Year Published: 2010	Bisphosphonates are first-line treatment; raloxifene can be helpful for vertebral fractures but uncertain benefit for nonvertebral fractures; teriparatide used for high risk-patients for no more than 2 years; estrogen should be used primarily for menopause symptoms and must carefully weigh benefit when menopause symptoms cease; calcitonin is second line because it is less effective than other agents.
Author: Papaioannou, et al[65] Organization: Scientific Advisory Council of Osteoporosis Canada Year Published: 2010	Risedronate, alendronate, zoledronic acid, denosumab, and raloxifene are all considered first-line treatments for post-menopausal women with osteoporosis, and hormone therapy is considered to be a first-line treatment for post-menopausal women who are experiencing vasomotor symptoms; etidronate and calcitonin are considered to be options for those intolerant of first-line treatments.
Author: Compston, et al[66] Organization: National Osteoporosis Guideline Group (UK) Year Published: 2009	Alendronate is first choice due to generic availability; if alendronate is not tolerated or is contraindicated, other bisphosphonates, strontium ranelate, or raloxifene are options; teriparatide should be reserved for those at very high risk because of its cost.
Author: Kanis, et al[67] Organization: International Osteoporosis Foundation and European Society for Clinical and Economic Evaluation of Osteoporosis and Osteoarthritis Year Published: 2008	Multiple agents can be used depending on the needs of the patient; alendronate, risedronate, and strontium are the only agents considered effective for hip fracture; calcitonin is a second-line agent.
Author: Qaseem, et al[68] Organization: American College of Physicians Year Published: 2008	Choice of therapy is recommended to be based on individual patient needs; bisphosphonates considered first line because of benefit for vertebral, non-vertebral, and hip fractures; many other medications considered to have good evidence for vertebral fractures.

studies comparing agents. As some guidelines note, there are no randomized, controlled trials that compare agents head-to-head for efficacy. Some retrospective studies have been completed, and those involving risedronate were included in the "Head-to-Head Studies" portion of the "Clinical Studies" section of this paper. There is also limited data to make full economic comparisons of the agents. The largest body of economic research has focused on alendronate and risedronate, as noted above in the "Cost Effectiveness for Hip Fracture" section. Two guidelines recommend alendronate as the first-line treatment, with one of these specifically citing alendronate's generic availability as a benefit.[62,66] Some guidelines also recommend that teriparatide be reserved for patients at highest risk because of its cost.[63,66]

Based on guidelines, risedronate is one of the first-line treatments to prevent hip fracture. As noted above, comparing risedronate against all other treatments that can prevent hip fracture is difficult because of limited head-to-head data. However, available information provides some useful insight when choosing between agents for individual patients. As noted previously in the "Head-to-Head Studies" section, comparisons between risedronate and alendronate for efficacy and cost effectiveness have had mixed results, making it less clear on a population basis if one medication is clearly a better choice. However, the availability of generic alendronate may be beneficial for patients who are bearing the cost of the medication. There is some evidence that risedronate may have better GI tolerability than alendronate and therefore may be preferred over alendronate for some patients. For patients needing an oral medication who have difficulty with tolerability, strontium may be less likely to cause gastrointestinal issues than bisphosphonates based on its side effect profile from placebo-controlled studies, but it has not been compared with bisphosphonates head-to-head. Risedronate's availability in different oral dosage regimens offers potential options for patients who have difficulty with adherence and is a potential advantage over medications such as strontium that require daily dosing. However, a discussion between a healthcare provider and the patient is important to determine if less frequent oral administration would be easier or more difficult for the patient to remember or if medications that can be administered directly by healthcare providers, such as intravenous bisphosphonates or denosumab, may be the best option for adherence. At this point there is insufficient data to compare the efficacy of oral risedronate to the intravenous bisphosphonates, but consideration of the patient's tolerability of an oral versus an intravenous agent is an important consideration because there are potential differences in side effects between the two dosage forms. As noted previously, denosumab may potentially be more cost effective than bisphosphonates for patients who have difficulty with adherence,[35] but this needs further study.

Conclusion

Risedronate is an effective treatment for hip fracture in postmenopausal women and for some patients may have advantages over other bisphosphonates. However, before initiating treatment with risedronate, it is important to carefully evaluate the patient's need and appropriateness for therapy. Data from trials indicate that risedronate does not have benefit for hip fracture for patients who are not at risk for fracture, and results show that advanced age alone is not a reason for treatment. Therefore, careful evaluation of a patient's risk for fracture using FRAX or other available screening tools is important. Potential medication adverse reactions must also be considered. Risedronate has been tolerated well in clinical trials, but an individual patient's co-morbidities and previous medication sensitivities (such as gastrointestinal toleration of medications) are important. Serious side effects of risedronate and other bisphosphonates are rare but could have significant consequences for some patients with co-morbidities. The poor adherence to bisphosphonates found in studies may warrant discussion of side effects and patient concerns. When patients are appropriately considered for treatment, risedronate represents a useful option in the prevention of hip fracture in postmenopausal women.

Disclosures

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