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Long-Term Tolerability of the Bisphosphonates in Postmenopausal Osteoporosis

A Comparative Review

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Contents

Abstract

Osteoporosis in postmenopausal women is a growing health concern for society. Bisphosphonates have become the mainstay of prevention and treatment with the mounting evidence of their efficacy over the past two decades.

This review article examines the use of the etidronate, alendronate and risedronate. The pivotal trials are reviewed for long-term tolerability, evidence regarding histological safety and gastrointestinal tolerance. Etidronate, alendronate and risedronate have also been examined in meta-analyses, which reviewed methodologically sound trials. Length of treatment, adverse events and medication discontinuation and patients lost to follow-up were evaluated.

Etidronate trials and the recent meta-analysis support the safe clinical use of cyclical etidronate with no signs of osteomalacia or other skeletal pathology over 2 to 3 years. In addition to increased bone mineral density (BMD) and vertebral fracture risk reduction, patients tolerated cyclical etidronate well up to 4 years in randomised studies. Non-randomised data has shown safety up to 7 years with clinical and bone biopsy data.

Alendronate studies demonstrated similar overall adverse event rates, study discontinuation rates and loss to follow-up rates between placebo and treatment arms, in addition to consistent improvements in BMD, vertebral and non-

vertebral fracture risk reductions over 3 to 4 years. Histological safety has been demonstrated up to 3 years. Longer-term therapy in non-randomised trials up to 7 years showed similar clinical safety between alendronate and placebo.

Risedronate trials and the meta-analysis also showed similar adverse event profiles between placebo and treatment arms, as well as improvements in BMD, vertebral and non-vertebral fracture risk reductions up to 3 years. Rates of discontinuation due to gastrointestinal events were similar between groups. Histological safety has also been demonstrated for risedronate up to 3 years.

Each of these bisphosphonates have been shown to have comparable safety with placebo up to 3 to 4 years, with the most rigourous trials carried out for alendronate and risedronate. Long-term comparative studies are awaited.

Osteoporosis is a major health concern, affecting a growing number of individuals worldwide. Mortality from hip fractures alone has been estimated at 12 to 20% in the first year after fracture. With this evident mortality and associated morbidity, the health and long-term care costs associated with osteoporosis-related fractures are enormous.[1] The disorder is characterised by low bone mass and bone fragility, resulting in an increased risk of fracture. Since the end result is fracture with little or no trauma, early diagnosis and treatment is of paramount importance. Bone mineral density (BMD) measurements have been established to assist in the detection of asymptomatic disease. If the BMD is less than 2.5 standard deviations, there is bone density evidence of osteoporosis. Based on these criteria, it has been estimated that as many as 30% of postmenopausal women have osteoporosis.[2]

Bisphosphonates have become the mainstay of prevention and treatment of osteoporosis with a number of studies supporting their use over the past two decades. Pamidronate, clodronate and tiludronate are available in some countries. However, these medications are not available as oral formulations approved for the management of osteoporosis in Canada and the US. The oral formulations of bisphosphonates, etidronate, alendronate and risedronate are the key agents within this class that have been used clinically for the management of postmenopausal osteoporosis. This article examines the use of the latter three agents in light of their long-term tolerability in postmenopausal osteoporosis.

1. Etidronate

The initial oral agent in the prevention and treatment of osteoporosis, etidronate is a well-known medication. The most common concerns outlined from initial studies were diarrhoea, nausea and flatulence. Serious concerns related to osteomalacia have been abated with cyclical therapy.[3] The instructions for medication administration are to take each tablet with plenty of water at bedtime, 2 hours before or after eating.[3]

1.1 Pivotal Trials

The two significant trials discussed in detail are described in table I. Storm et al.[4] found a significant increase in vertebral bone mineral content (BMC) and a significant reduction in new vertebral fractures in the etidronate treatment arm compared with placebo over the 3-year study. No significant adverse events related to etidronate were observed. However, of the 26 (39.4%) patients lost to follow up (LTF), six from each treatment group withdrew voluntarily or related to non-compliance, and five from each group died. The remaining withdrawals were two from each group related to intercurrent illness. Although these are a large number of patients related to the total sample size, the effects were equal in both etidronate and placebo groups. In addition, bone biopsies at 60 and 150 weeks were done and no signs of osteomalacia or other skeletal pathology were detected.

Watts et al.[8] also found a significant increase in vertebral BMD and a significant reduction in

Table I. Characteristics of pivotal bisphosphonate studies

Trial[5-7]	No. of patients randomised (treatment/ control)	Patients (baseline age; baseline BMD; T-score)	Intervention	Comparison	Duration (y)	Outcomes	Loss to follow-up
Etidronate							
Storm et al.[4]	66 (33/33)	68.3; BMC = 25.1g	Etidronate 400 mg/day for 14 days in 91-day cycle	Placebo	3	BMC: lumbar, distal forearm. Fractures: vertebral, non-vertebral	26/66 (39.4%)
Watts et al.[8]	423 (212/211)	65.1; 0.86 g/cm^2	Etidronate 400 mg/day for 14 days in 91-day cycle	Placebo ± phosphorus	2	BMD: lumbar, femoral neck, trochanter, ward's triangle, distal radius. Fractures: vertebral, non-vertebral	60/423 (14.2%)
Alendronate							
Black et al.[9]	2027 (1022/1005)	71.0; 0.57 g/cm^2; –2.3	Alendronate 5 mg/day × 2y, then 10 mg/day × 1y	Placebo	3	BMD: lumbar spine, femoral neck, total hip, trochanter, total body. Fractures: vertebral, non-vertebral, hip, wrist	78/2027 (3.8%)
Cummings et al.[10]	4432 (2214/2218)	67.6; 0.59 g/cm^2; –3.1	Alendronate 5 mg/day × 2y, then 10 mg/day	Placebo	4	BMD: lumbar spine, femoral neck, total hip, trochanter, distal forearm. Fractures: vertebral, non-vertebral	160/4432 (3.6%)
Pols et al.[11]	1908 (950/958)	62.8; 0.63 g/cm^2; –2.7	Alendronate 10 mg/day	Placebo	1	BMD: lumbar, femoral neck, trochanter, total hip. Fractures: non-vertebral	211/1908 (11.1%)
Risedronate							
Harris et al.[12]	2458 (1638/820)	68.7; 0.83 g/cm^2; –2.0	Risedronate 2.5 or 5 mg/day	Placebo + vitamin D 500IU (if 25-hydroxy vitamin D levels were low)	3 (2.5 mg/day dose arm discontinued at 1y)	BMD: lumbar, femoral neck, trochanter. Fractures: vertebral, non-vertebral	1y: 611/2458 (24.9%) 3y: 708/1647 (43.0%)
Reginster et al.[13]	1226 (819/407)	71.0; 0.79 g/cm^2; –2.7	Risedronate 2.5 or 5 mg/day	Placebo + vitamin D 500IU (if 25-hydroxy vitamin D levels were low)	3 (2.5 mg/day dose arm discontinued at 2y)	BMD: lumbar, femoral neck, trochanter. Fractures: vertebral, non-vertebral	451/1226 (36.8%)
McClung et al.[14]	9331 (6197/3134)	77.7; –3.7	Risedronate 2.5 or 5 mg/day	Placebo + vitamin D ≤500IU (if 25-hydroxy vitamin D levels were low)	3	Fractures: hip, non-vertebral. BMD: femoral neck, trochanter	3324/9331 (35.6%)

BMC = bone mineral content; **BMD** = bone mineral density.

vertebral fractures in the combined etidronate arm of this 2-year, placebo-controlled study. This study design included groups with phosphate, but in the final analysis, the addition of phosphate provided no apparent benefit. There were no significant differences in adverse events between combined etidronate and combined placebo groups. Of the 60 (14.2%) patients LTF, four from the combined etidronate arm and three from the combined placebo arm, withdrew related to adverse reactions. The remainder included 18 voluntary withdrawals, seven uncooperative or loss of interest, two who died of unrelated causes, and 26 with intercurrent illnesses. In addition, bone biopsies done in 55 patients (combined etidronate arm: 27 and combined placebo arm: 28) at entry and at 2 years did not demonstrate any mineralisation defects or other skeletal pathology.

1.2 Meta-Analysis

A recently published meta-analysis[5] examined the effect of etidronate on bone density and fractures in postmenopausal women. This detailed search identified 358 articles via electronic search strategy and six from hand-searching, and included 13 trials, with a total of 1267 postmenopausal women. These were randomised clinical trials of at least 1 year's duration comparing etidronate with placebo or calcium and/or vitamin D, with outcomes including fracture incidence or bone density. All trials used intermittent cyclical method of etidronate at 400 mg/day for 14 to 20 days followed by 56 to 91 days of calcium and/or vitamin D. Three independent reviewers evaluated methodological quality and abstracted data. While this review demonstrated etidronate, relative to control, increased BMD after 1 to 3 years, effects were even larger at 4 years. In addition, there was a suggestion of vertebral fracture reduction, but not with non-vertebral fractures. Of these 13 studies, details of patients who dropped out or withdrew were available for eight. Importantly, the pooled estimates showed no statistical difference between placebo and etidronate for the risk of withdrawal due to adverse events [0.93, 95% confidence interval (CI) 0.70 to 1.23, p = 0.59, heterogeneity p-value 0.68] or for dropouts overall (1.30, 95% CI 0.58 to 2.93, p = 0.53, heterogeneity p-value 0.68).

With etidronate therapy, longer-term safety than 4 years has been established in non-randomised trials. A 7-year study showed no appreciable differences than the trials in the above meta-analysis.[15] This study also demonstrated histological safety with 7-year bone biopsies following cyclical etidronate therapy. However, it was excluded from the meta-analysis due to its lack of methodological rigour. Therefore, with appropriate medication administration of etidronate, long-term tolerability can be demonstrated.

2. Alendronate

The main concern with the aminobisphosphonate, alendronate, is gastrointestinal toxicity. As a result, case reports and endoscopic studies[16,17] have been published evaluating this. The most common issues have been abdominal pain, nausea, dyspepsia, constipation and diarrhoea. The most concerning lesions have been oesophageal ulcers and gastritis.[18] This perception of clinical gastrointestinal intolerance has been perpetuated by case reports and endoscopic studies mentioned above,[16,17] and by others,[19-21] where approved medication administration instructions (swallowing each tablet with a full glass of plain water and not lying down for at least 30 minutes and before the first food, beverage or other medication of the day[18]) or contraindications may not have been adhered to. In addition, in many cases, these studies were of lesser methodological quality compared with some of the trials considered in section 2.1.

2.1 Pivotal Trials

The trial characteristics of the two FIT (Fracture Intervention Trial) studies[9,10] and the FOSIT (Fosamax International Trial) study[11] are outlined in table I. In the first FIT study, Black et al.[9] found a significant increase in BMD and a significant reduction in both, vertebral and non-vertebral fractures over this 3-year study. There were no signif-

icant differences in overall adverse event rates. Patients receiving alendronate [422 (41.3%)] versus patients receiving placebo [402 (40.0%)] reported similar incidences of upper gastrointestinal adverse events. There was also no increase in these event rates during the increased dose phase of the study at 10 mg/day. Patients were well accounted for with only 78 (3.8%) patients LTF. No significant difference in patients who discontinued study medication secondary to adverse events was demonstrated [alendronate: 78 (7.6%) versus placebo: 96 (9.6%)].

Cummings et al.[10] also found a significant increase in BMD and a reduction in both vertebral and non-vertebral fractures, although not statistically significant, over the 4-year second FIT study. There were no significant differences in total adverse event rates between groups. Patients receiving alendronate [1052 (47.5%)] versus patients receiving placebo [1047 (47.2%)] also reported similar upper gastrointestinal adverse events. Patients were well accounted for with only 160 (3.6%) patients LTF. No significant difference in patients who discontinued study medication secondary to adverse events was demonstrated [alendronate: 221 (9.9%) versus placebo: 227 (10.2%)]. The above two FIT studies excluded patients with previous major upper gastrointestinal tract erosive disease, including recurrent or recent upper gastrointestinal tract bleeding, at study entry. However, similar proportions of patients taking alendronate [453 (14.0%)] versus placebo [472 (14.6%)] had histories of upper gastrointestinal disease. In addition, the use of nonsteroidal anti-inflammatory agents was similar at baseline and throughout the study in both groups.[22]

In the multinational FOSIT study, Pols et al.[11] also found a significant increase in BMD over 1 year. This study did not establish fracture risk as an *a priori* efficacy parameter due to lack of power. However, in the data collected, a significant reduction in non-vertebral fractures was found. There was no significant difference in overall adverse events. Upper gastrointestinal adverse events were not significantly different between groups [alendronate: 202 (21.3%) patients versus placebo: 185 (19.3%) patients]. In total, 211 (11.1%) patients were LTF. No significant difference was demonstrated when comparing the treatment group (6.4%) and the control group (5.6%) for patients who discontinued study medications secondary to adverse events.

2.2 Meta-Analysis

Many studies have been completed examining the efficacy and safety of alendronate in postmenopausal women. Subsequently, a meta-analysis has reviewed the effect of alendronate on bone density and fractures in postmenopausal women.[6] This detailed and exhaustive search examined 358 articles and abstracts, and included 11 randomised placebo-controlled clinical trials involving a total of 12 855 postmenopausal women. Follow-up was for at least 1 year and the trails included fracture incidence or BMD data. All trials used daily alendronate therapy with doses ranging from 5 to 40mg. Three independent reviewers evaluated methodological quality and abstracted data with moderate to high level agreement. A consistent improvement in vertebral and non-vertebral fracture risk was observed, especially for daily doses 10mg or greater. In addition, consistent improvement in BMD was found favouring alendronate, especially at doses 10mg or greater. In these 11 studies, dropout rates were the only area of heterogeneity in study methodology. Importantly, the pooled estimate of the relative risk of discontinuing medication as a result of adverse events from eight trials using 5mg of alendronate or greater of 1.15 (95% CI 0.93 to 1.42) was very consistent across trials (heterogeneity p-value 0.82).

Another important issue has been alternate administration regimens. A recent randomised controlled study compared efficacy and safety of alendronate 70mg once weekly (519 patients) with 35mg twice weekly (369 patients) and 10mg daily (370 patients).[23] A total of 1258 postmenopausal patients of a mean age at baseline of 66.5 years participated in this 1-year study. Baseline BMD at the lumbar spine was 0.74 g/cm^2. In this study, as

with the pivotal trials and meta-analysis, there were significant increases in BMD. The two new regimens fully satisfied the equivalence criteria relative to daily therapy. In addition, all treatments were well tolerated with a similar incidence of upper gastrointestinal adverse events. Overall, the once weekly regimen was found to be therapeutically equivalent with a similar adverse effect profile to the once-daily regimen.

Longer-term therapy past 4 years has been established in non-randomised trials. An initial 3-year study with two 2-year open-label extensions has lead to an alendronate study of 7 years in length.[24] This trial has showed similar adverse event profiles when compared with the more methodologically sound studies. Alendronate in doses of 5mg or less has been studied in a prospective, 2-year, randomised and blinded fashion in elderly patients (mean age approximately 70 years) with favourable results with respect to gastrointestinal tolerance.[25] Another study has demonstrated histological safety up to 3 years.[26] With this information in mind, patients without significant gastrointestinal disease should be able to tolerate alendronate safely provided the administration instructions are followed as demonstrated in the studies presented. Upper gastrointestinal adverse events may be related to the population of postmenopausal women with osteoporosis, as patients who previously failed alendronate treatment were blindly re-challenged with alendronate or placebo with similar outcomes with respect to upper gastrointestinal adverse events between groups.[27] The results of this study suggest that many of these upper gastrointestinal adverse events reported during therapy with alendronate may reflect a high background incidence of these complaints and an increased sensitivity to detection of such complaints, rather than a causal relationship to therapy. Patient education on directions for taking alendronate are important and require reinforcement both verbally and with written instructions to ensure adherence.

3. Risedronate

The newest of the bisphosphonates, the pyridinyl bisphosphonate risedronate, has also had concerns related to gastrointestinal toxicity. The most common concern with this medication has been abdominal pain.[28] Although concern about clinical gastrointestinal intolerance has been perpetuated with little evidence, the administration instructions are nevertheless important to prevent adverse events. Similar to alendronate, the risedronate administration instructions are to take each tablet with a half a glass of plain water and not lying down for at least 30 minutes and before the first food, beverage or other medication of the day or at another time during the day with 2 hours before or after eating or drinking.[28]

3.1 Pivotal Trials

The trial characteristics for the two Vertebral Efficacy with Risedronate Therapy (VERT) studies are outlined in table I. In the first VERT study, Harris et al.[12] demonstrated a significant reduction in vertebral and non-vertebral fractures along with a significant increase in BMD from baseline in the risedronate 5 mg/day group versus placebo in this 3-year North American study. Risedronate 2.5 mg/day was studied only during the first year of this trial, and then discontinued. Data for this arm were not reported in detail. Adverse events were similar across risedronate 5 mg/day and placebo groups, including upper gastrointestinal tract adverse events [245 (30.1%) risedronate recipient versus 219 (26.9%) placebo recipients]. A large number of patients were LTF [1 year: 611 (24.9%) and 3 year: 708 (43.0%)]. Sixty percent of participants in the 5 mg/day risedronate group and 55% of participants in the placebo group completed 3 years of treatment. In an analysis of this, including incidence of adverse events, no significant differences were found for withdrawals. The one exception was a substantially higher proportion (19.6%) of patients in the placebo group who experienced vertebral fractures compared with the proportion (10.6%) of patients in the 5 mg/day risedronate

group. Withdrawals related to adverse events were not found to be different [risedronate 5 mg/day: 138 (17.0%) patients versus placebo: 136 (16.7%) patients]. In addition, bone biopsies done in 62 patients (risedronate 5 mg/day: 31 and placebo: 31) at entry and at 3 years did not demonstrate any osteomalacia or other skeletal pathology.

In the second VERT study, Reginster et al.[13] found a significant reduction in vertebral fractures and significant increases in BMD from baseline in the risedronate 5 mg/day group versus placebo over this 3-year multinational study. The reduction of non-vertebral fracture approached statistical significance (p = 0.06). Risedronate 2.5 mg/day was studied only during the first 2 years of this trial, and then discontinued. Adverse events were similar across groups, including upper gastrointestinal tract adverse events [risedronate 5 mg/day: 109 (26.8%) patients versus placebo: 104 (25.5%) patients]. A large number of patients were LTF [451 (36.8%)]. Sixty-two percent of participants in the 5 mg/day risedronate group and 54% of participants in the placebo group completed 3 years of treatment. No specific analysis of this difference was articulated. Withdrawals related to adverse events were not found to be different between groups [risedronate: 5 mg/day: 63 (15.5%) patients versus placebo: 81 (19.9%) patients].

McClung et al.[14] found that risedronate 2.5 or 5 mg/day significantly reduced the risk of hip fracture among elderly women with confirmed osteoporosis (n = 5445), but not among elderly women selected primarily on the basis of risk factors (n = 3886) over a 3-year study period. Adverse events were similar across groups, including adverse events involving the upper gastrointestinal tract [risedronate 5 mg/day: 657 (21.2%) patients versus risedronate 2.5 mg/day: 690 (22.3%) patients versus placebo: 684 (21.8%) patients] even in patients 80 years of age and older. A large number of patients were LTF [3324 (35.6%)]. Fifty percent of participants in the combined risedronate arm and 51% of participants in the placebo arm completed 3 years of treatment. Patients who discontinued early were thought to be at higher risk for hip fracture based on their demographics. Discontinuation of treatment due to adverse events was not found to be different between groups [risedronate: 5 mg/day: 550 (17.7%) patients versus risedronate 2.5 mg/day: 548 (17.7%) patients versus placebo: 564 (18.0%) patients].

3.2 Meta-Analysis

A number of studies have been completed examining the efficacy and safety of risedronate in postmenopausal women. Subsequently, a meta-analysis has reviewed the effect of risedronate on bone density and fractures in postmenopausal women.[7] This thorough search examined 18 articles and included eight randomised, placebo-controlled clinical trials of a total of 14 832 postmenopausal women with follow-up of at least 1 year; and included fracture incidence or BMD data. All trials used daily or cyclical risedronate therapy with doses ranging from 2.5 to 5mg. Two independent reviewers evaluated methodological quality and abstracted data with a high level of agreement. A consistent improvement in vertebral and non-vertebral fracture risk was found, especially for the daily dose of 5mg. In addition, consistent improvement in BMD was found favouring risedronate, especially at daily doses of 5mg. In these eight studies, dropouts and withdrawals was the only area of heterogeneity in study methodology. In fact, three studies had losses to follow up of over 30%. When this was examined more closely for bias, these instances favoured the control groups when compared to the treatment groups. With this in mind, treatment had little or no impact on the risk of discontinuing medication (relative risk 0.94, 95% CI 0.80 to 1.10). For discontinuation due to gastrointestinal adverse events, the pooled relative risk was 0.97 (95% CI 0.90 to 1.04). The pooled relative risks for dyspepsia, and abdominal pain were similar. For oesophagitis, the pooled relative risk from five trials was 0.91 (95% CI 0.70 to 1.18).

Risedronate in the above systematic review demonstrates a safety profile similar to placebo following 3 years of treatment when adhering to

the approved medication administration regimens. A study which examined bone biopsies in patients treated with risedronate or placebo found no histological abnormalities at 1 year.[29] In addition, the generalisability of the risedronate trials may be greater than earlier bisphosphonate trials because patients with a prior history of peptic ulcer disease or those using aspirin (acetylsalicylic acid) or non-steroidal anti-inflammatory agents participated in more studies.

4. Comparisons

Few comparative studies have been performed. One study[30] of less than 100 patients compared cyclical etidronate with daily alendronate. Although, statistically significant gastrointestinal adverse events were seen with alendronate, this group of patients received the most benefit in changes of BMD in this 18-month study. A multicentre, placebo-controlled, randomised clinical trial of endoscopic changes at 28 days with alendronate 40 mg/day versus risedronate 30 mg/day found similarly low gastroduodenal irritation rates.[31] Further sound clinical studies are awaited to support or refute these findings.

The belief with bisphosphonate therapy has been that gastrointestinal intolerance to one agent means that this is a class effect. To study this further, a recent randomised study of 3 months duration studied 66 postmenopausal women who had previously discontinued therapy with alendronate 10 mg/day due to upper gastrointestinal intolerance.[32] The patients were then randomised to risedronate 5 mg/day or placebo. Both rates of discontinuation and overall incidence of adverse events secondary to upper gastrointestinal adverse events were similar in both risedronate and placebo groups. These results are consistent with previous studies showing that risedronate has a gastrointestinal tolerability similar to that of placebo. In addition, intolerance to one bisphosphonate does not imply intolerance to others.

There is some suggestion that in the long-term, oversuppresion of bone may be deleterious to skeletal health.[33] While this remains a theoretical concern, there have not been any studies that demonstrate an increase in fractures with these more potent bisphosphonates.

5. Corticosteroid-Induced Osteoporosis

Many of the patients affected by corticosteroid-induced osteoporosis include the subgroup of postmenopausal women. A number of pivotal trials have studied the use of bisphosphonates in corticosteroid-induced osteoporosis.[34-37] In these studies, the number of postmenopausal women was over 40% of the study populations. Cyclical etidronate, alendronate and risedronate have been shown to increase BMD and reduce vertebral fracture rates in these trials and in subsequent reviews.[38] Importantly, through these studies continued safety has been demonstrated with adverse effects being similar between control and treatment groups.

6. Conclusion

The safety profiles of etidronate, alendronate, and risedronate have been established reliably for as long as 3 to 4 years in methodologically sound studies, as demonstrated in the pivotal studies and systematic reviews covered in this paper. Seven-year safety has also been demonstrated for etidronate and alendronate in non-randomised studies. There have been significant strides made to ensure safety, especially with the two newer agents (alendronate and risedronate), which have demonstrated the most concrete benefits in vertebral and non-vertebral fracture risk reduction. With these newer agents, more rigourous studies have been performed which have not demonstrated an increase in discontinuation related to adverse events when compared with controls. The comparative safety of these agents is yet to be well established with long-term safety data.

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