ORIGINAL RESEARCH ARTICLE

Clin Drug Invest 2006; 26 (2): 63-74
1173-2563/06/0002-0063/$39.95/0

Alendronic Acid Produces Greater Effects than Risedronic Acid on Bone Density and Turnover in Postmenopausal Women with Osteoporosis

Results of FACTS[1]-International

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Abstract

Background: The objective of the study was to evaluate the effects of alendronic acid once weekly relative to risedronic acid once weekly on bone mineral density (BMD), markers of bone turnover and tolerability in the treatment of osteoporosis in postmenopausal women.

Methods: This was a randomised, double-masked, double-dummy multicentre international study (75 centres in 27 countries in Europe, the Americas and Asia-Pacific). A total of 1303 women were screened and 936 with low bone density (T-score ≤−2.0 at the spine, hip trochanter, total hip or femoral neck) were randomised; 91% (n = 854) completed the study. Patients were randomised to treatment with either active alendronic acid 70mg weekly (Fosamax®) and placebo identical to risedronic acid weekly or active risedronic acid 35mg weekly (Actonel®) and placebo identical to alendronic acid weekly for 12 months. The primary efficacy endpoint was the percentage change from baseline in hip trochanter BMD at 12 months. Secondary endpoints included the percentage change from baseline in lumbar spine, total hip and femoral neck BMD; biochemical markers of bone turnover (including serum bone-specific alkaline phospha-

1 Fosamax Actonel Comparison Trials.

tase [BSAP] and urinary type I collagen N-telopeptides [NTx]); and safety and tolerability as assessed by reporting of adverse experiences.

Results: Alendronic acid produced greater increases in BMD than did risedronic acid at 12 months at all sites measured. Mean percentage increases from baseline in hip trochanter BMD at month 12 were 3.56% and 2.71% in the alendronic acid and risedronic acid groups, respectively (treatment difference [95% CI]: 0.83% [0.22, 1.45; p = 0.008]). Mean percentage increases from baseline were greater with alendronic acid than risedronic acid at the lumbar spine, total hip and femoral neck BMD at month 12 (p = 0.002, p < 0.001, p = 0.039, respectively). Increases in BMD with alendronic acid compared with risedronic acid were also significantly greater at 6 months at the trochanter and total hip. There was a greater reduction in bone turnover with alendronic acid compared with risedronic acid: NTx decreased 58% with alendronic acid compared with 47% with risedronic acid at 12 months (p < 0.001); and BSAP decreased 45% with alendronic acid compared with 34% with risedronic acid at 12 months (p < 0.001). Overall tolerability and upper gastrointestinal tolerability were similar for both agents.

Conclusions: Alendronic acid once weekly produced greater BMD increases at both hip and spine sites and greater reductions in bone turnover relative to risedronic acid once weekly. Both agents were well tolerated with no significant difference in upper gastrointestinal adverse experiences. Clinicians should consider these results when making treatment decisions for postmenopausal women with osteoporosis.

Introduction

The pathophysiology of osteoporosis involves increased bone turnover and an excess of bone resorption over formation, leading to decreases in bone density, reduced bone strength and increased fracture risk. The bisphosphonates alendronic acid and risedronic acid are currently the preferred therapy for the treatment of osteoporosis.[1] These agents effectively decrease bone resorption, increase bone mineral density (BMD), and reduce the risk of both vertebral and nonvertebral fractures. The magnitude of change in bone turnover and BMD during antiresorptive therapy has been correlated with the reduction in fracture risk.[2-10] Among antiresorptive agents, only those that produce relatively large effects on BMD and bone turnover (such as alendronic acid and risedronic acid) have convincingly demonstrated reductions in both vertebral and nonvertebral fracture risk.

Alendronic acid (Fosamax®, Merck & Co., Inc., Whitehouse Station, NJ, USA)[2] is a nitrogen-containing bisphosphonate that selectively inhibits osteoclast-mediated bone resorption. Large placebo-controlled clinical trials have reported BMD increases of approximately 9% at the spine and 6% at the hip with alendronic acid 10mg daily for 3 years.[11,12] Long-term follow-up of the phase III studies of alendronic acid have demonstrated that spine BMD increases progressively for at least 10 years, and the initial BMD increases with alendronic acid treatment at other skeletal sites are maintained during long-term therapy.[13,14] In addition, bone turnover markers are reduced to the normal premenopausal range within months, and remain stable for at least 10 years, without evidence of progressive declines.[13,14] Treatment with alendronic acid also reduces the relative risk of vertebral fractures by 48% compared with placebo consistently across studies that included different populations; a

2 The use of trade names is for product identification purposes only and does not imply endorsement.

37–55% relative risk reduction was also observed for nonvertebral (including hip) fractures across different populations with osteoporosis.[15,16] These fracture risk reductions were observed within 6–18 months after initiating therapy.[17-19]

Risedronic acid (Actonel®, Procter & Gamble Pharmaceuticals and Sanofi-Aventis, Paris, France) is a pyridinyl bisphosphonate that, like alendronic acid, binds to bone hydroxyapatite and inhibits osteoclast-mediated bone resorption. In postmenopausal women with osteoporosis and prior vertebral fracture, increases in BMD over 3 years with risedronic acid 5mg daily were approximately 5% at the lumbar spine, 2% at the femoral neck, and 3% at the hip trochanter.[20] Reductions in biochemical markers of bone turnover during daily risedronic acid therapy were also observed,[20] albeit to a lesser extent than the reductions achieved with alendronic acid, but such differences may be partly related to different assay techniques or other factors. Vertebral and nonvertebral fracture risk reductions of approximately 36% and 27%, respectively, have been reported in a meta-analysis of data from randomised trials of risedronic acid in women with osteoporosis.[21] As with alendronic acid, fracture risk reductions were observed within the first year of risedronic acid treatment.

Direct head-to-head studies with clinically relevant endpoints are the best method by which to compare the efficacy of different therapeutic agents.[21] An ideal comparison of agents for osteoporosis would include fracture as an endpoint. However, such a study is impractical due to the enormous cost and resources that would be required. For instance, more than 50 000 patients would be required to show a difference in fracture rates of at least 10%, assuming a 1-year fracture incidence of 5%.[22] In the absence of head-to-head fracture data, comparative studies with validated surrogate endpoints provide alternative evidence.[23,24] Measurements of BMD and bone turnover markers are appropriate surrogates, since the magnitude of change in these measures during treatment with antiresorptive agents is associated with relative reductions in fracture risk.[3,10]

Alendronic acid produced significantly greater increases in BMD and reductions in biochemical markers of bone turnover than risedronic acid in two head-to-head studies. In the first trial, patients were randomised to alendronic acid 70mg taken once weekly while fasting or risedronic acid 5mg taken daily 2 hours after a meal (as suggested by the manufacturer and approved in most countries).[25] Subsequently, weekly dosing with risedronic acid 35mg became available and was used in the second trial, conducted in the US.[26] In any area of research, consistent confirmatory results from at least two studies are much more convincing than results from a single study. Therefore, the present international study, similar in design to the earlier US study, was undertaken to directly compare the efficacy and tolerability of once-weekly alendronic acid and once-weekly risedronic acid in postmenopausal women with osteoporosis.

Methods

Study Design

This double-blind, randomised, active-controlled, multicentre study (protocol 907) was conducted at 75 sites in 27 countries throughout Europe, the Middle East, the Americas and Asia-Pacific. This study was conducted in accordance with consideration for the protection of patients, as outlined in the Declaration of Helsinki, and investigators obtained approval from the appropriate ethical review committees. All patients provided written informed consent before entering the study.

Patients were community-dwelling, ambulatory, postmenopausal (≥6 months beyond the final menstrual period) women ≥40 years of age with low bone density (≥2.0 SD below the young normal mean based on the normal range provided by the densitometry manufacturer) at one or more of four sites (hip trochanter, lumbar spine, total hip or femoral neck) and who met prespecified entry criteria. Patients were required to be in good general health, and to have hip and spine anatomy suitable for dual energy x-ray absorptiometry (DXA). Reasons for exclusion included a history of abnormalities of the

oesophagus (such as stricture or achalasia) that delay oesophageal emptying and inability to remain upright for 30 minutes after administration, in accordance with the alendronic acid label. Patients with hypocalcaemia (serum calcium <8.5 mg/dL), hypovitaminosis D (serum 25(OH)D <10 ng/mL) or metabolic bone diseases other than postmenopausal osteoporosis were excluded from the study. Use of estrogen, estrogen analogues, tibolone or anabolic steroids within 6 months, any bisphosphonate within 1 year or for ≥2 years within 5 years, or any parathyroid hormone within the past year were also reasons for exclusion.

This was a 12-month trial with an additional 12-month extension during which patients were maintained on blinded study medicine; the first 12 months of the trial are reported here. Patients were recruited between March 2003 and October 2003; the last trial visit occurred in October 2004. Patients who met all study entry criteria were enrolled and randomly assigned to receive either alendronic acid 70mg once weekly and risedronic acid-matching placebo, or risedronic acid 35mg once weekly and alendronic acid-matching placebo. Assignment to treatment group was made using a computer-generated random allocation schedule generated by the study statistician. Numbered containers were used to implement allocation and each patient was assigned the next number in the sequence upon being enrolled. All study personnel, including investigators, study-site personnel, patients, monitors, central laboratory and DXA facility personnel, remained blinded to treatment allocation throughout the study; the code was revealed to the researchers once recruitment, data collection and laboratory analyses were complete for the 1-year extension. Patients were instructed to take the medication with 6–8 ounces of water prior to the first food or beverage of the day, and to remain in an upright position for 30 minutes following administration. Treatment was to begin within 7 days of randomisation and be taken on the same day each week. Patients were instructed to take 1000mg of elemental calcium and 400IU of vitamin D daily for the duration of the study, either from dietary sources or as a supplement.

Measurements

BMD at the posterior-anterior (PA) lumbar spine and proximal femur was measured by DXA at baseline (randomisation) and 6 and 12 months after randomisation using Hologic or Lunar densitometers. All BMD analyses were performed by a central analysis facility (Bio-Imaging Technologies, Inc., Newtown, PA, USA).

Laboratory parameters used to evaluate changes in bone turnover were urinary N-telopeptide of type I human collagen corrected for creatinine (NTx) [Ortho Vitros, Ortho Clinical Diagnostics, Amersham, UK] and serum C-telopeptide (CTx) [Roche Elecsys, as measured on the Elecsys 2010 automated analyser, Mannheim, Germany] to assess rate of bone resorption, and serum bone-specific alkaline phosphatase (BSAP) [Access OSTASE Assay, Beckman-Coulter, Fullerton, CA, USA] and serum N-terminal propeptide of type 1 procollagen (P1NP) [INTACT P1NP, Orion Diagnostic, P1NP RIA, Espoo, Finland] to assess rate of bone formation. The analyses of biochemical markers of bone turnover were performed by a central laboratory (Quest Diagnostics Clinical Trials Laboratory, Van Nuys, CA, USA).

Efficacy and Safety Evaluations

The primary efficacy endpoint was the percentage change from baseline in hip trochanter BMD at 12 months. The study was designed to enroll at least 860 patients to ensure at least 732 patients would be evaluated at the end; this would provide 90% power to detect a significant ($p < 0.05$) difference of 1.2% in the percentage change from baseline between groups, assuming an SD of 5.0%. Secondary endpoints included percentage change from baseline in lumbar spine, total hip and femoral neck BMD at 12 months, and percentage change in all BMD endpoints at 6 months.

The percentage of patients with predefined increases in hip trochanter and lumbar spine BMD ≥0% from baseline and those with ≥3% increase from baseline at 12 months were analysed. A separate subgroup analysis was conducted based on the patients who at baseline either met the WHO defini-

tion of osteoporosis (i.e. BMD T-score ≤−2.5) or had sustained a fracture of the wrist, hip or spine after the age of 45 years. Percentage change from baseline in biochemical markers of bone turnover (NTx, CTx, BSAP and P1NP) at 3, 6 and 12 months were also included as secondary efficacy endpoints.

Safety and tolerability were also included as a secondary endpoint, including an assessment of upper gastrointestinal adverse experiences (AEs). Safety was monitored by recording clinical and laboratory AEs. Patients could report AEs at any time during the study.

Statistical Analysis

BMD analyses were based on a modified intention-to-treat (MITT) approach, including all randomised patients who had taken at least one dose of study drug and had both a baseline and at least one post-randomisation BMD measurement. For missing values, the last on-treatment observation was carried forward. The percentage change in BMD between the treatment groups was compared using ANOVA, including factors for study centre and treatment group. Treatment differences and associated 95% CIs were estimated from the ANOVA model. Statistical analyses were performed using Statistical Analysis Software Version 8.02 (SAS Institute Inc., Cary, NC, USA). The percentage of patients with improvement in hip trochanter and lumbar spine BMD of ≥0% and ≥3% was compared between treatment groups using a Mantel-Haenszel test stratified for study centre. Statistical significance was declared if $p < 0.05$ (two-tailed), unless specified otherwise by the multiplicity adjustment. As there was only one analysis of the primary endpoint, no multiplicity adjustment was needed for the primary endpoint. To adjust for multiplicity in other analyses, combinations of closed-testing and Hochberg procedures were employed for secondary endpoints and treatment effects at earlier times. For example, statistical significance for secondary endpoints was considered only if the primary endpoint difference was significant.

Log-transformed fraction from baseline in biochemical markers of bone turnover was compared using ANOVA with terms for treatment and study centre. The primary method for analysis of the biochemical markers was a per-protocol approach, excluding protocol violators and noncompleters based on predefined criteria with no data carried forward.

The safety analysis included all patients who received at least one dose of study medication in either treatment group. Fisher's Exact test was performed to compare the proportion of patients with any AEs, serious AEs, discontinuations due to AEs, and upper gastrointestinal AEs.

Results

Patient Participation

Overall, 1303 postmenopausal women were evaluated for participation in this study, 936 of whom were randomised. A total of 468 (50%) patients were randomised to alendronic acid, and 468 (50%) were randomised to risedronic acid. In the alendronic acid and risedronic acid groups, respectively, 91.9% and 90.6% completed the study. Figure 1

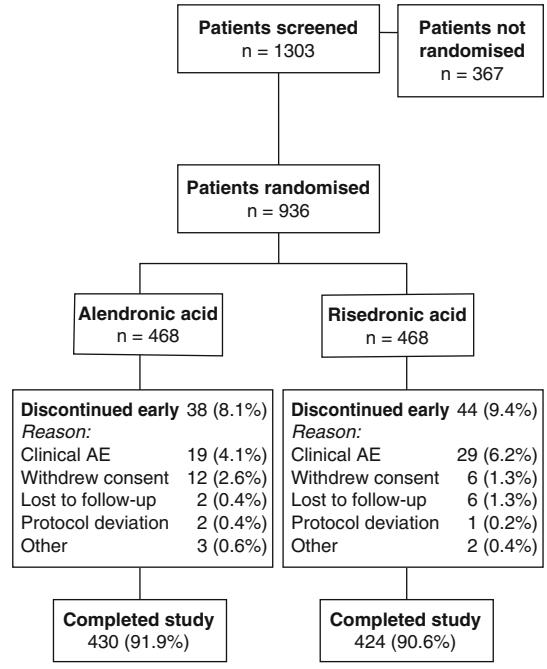

Fig. 1. Patient participation from screening to study completion. **AE** = adverse experience.

Table I. Demographics and baseline characteristics

Characteristic	Alendronic acid 70mg (n = 468)	Risedronic acid 35mg (n = 468)	Total (n = 936)
Age (y) [mean (SD)]	64.3 (8.1)	63.9 (8.3)	64.1 (8.2)
Race [n (%)]			
White	371 (79.3)	364 (77.8)	735 (78.5)
Hispanic	39 (8.3)	43 (9.2)	82 (8.8)
Asian	35 (7.5)	36 (7.7)	71 (7.6)
other	23 (4.9)	25 (5.3)	48 (5.1)
Age at menopause (y) [mean (SD)]	47.4 (5.5)	47.2 (5.7)	47.3 (5.6)
Time since menopause (y) [mean (SD)]	16.9 (9.5)	16.8 (9.4)	16.8 (9.5)
Family history of osteoporosis [n (%)]	152 (43.1)	139 (39.0)	291 (41.0)
Fracture history [n (%)]	166 (35.5)	149 (31.8)	315 (33.7)
BMD T-score [mean (SD)]			
hip trochanter	−1.56 (0.91)	−1.63 (0.91)	−1.60 (0.91)
total hip	−1.63 (0.81)	−1.73 (0.81)	−1.68 (0.81)
femoral neck	−2.06 (0.76)	−2.17 (0.75)	−2.12 (0.75)
lumbar spine	−2.63 (0.87)	−2.66 (0.88)	−2.64 (0.87)
Met WHO definition of osteoporosis[a] [n (%)]	339 (74.0)	350 (76.9)	689 (75.5)
Biochemical markers [mean (SD)]			
NTx (nmol/mmol)	48.4 (23.1)	47.4 (23.6)	47.9 (23.3)
CTx (ng/mL)	0.425 (0.2)	0.423 (0.2)	0.424 (0.2)
BSAP (μg/L)	15.2 (5.1)	15.7 (6.1)	15.5 (5.6)
P1NP (μg/L)	53.2 (22.0)	52.9 (22.9)	53.0 (22.4)

a T-score ≤−2.5 at any site or hip, spine or wrist fracture after age 45 years.

BMD = bone mineral density; **BSAP** = serum bone specific alkaline phosphatase; **CTx** = serum C-telopeptide; **NTx** = urinary N-telopeptide of type I human collagen corrected for creatinine; **P1NP** = serum N-terminal propeptide of type 1 procollagen.

illustrates patient participation from screening to study completion.

Baseline Characteristics

The demographic and baseline characteristics were similar between treatment groups (table I). The mean age was 64.1 years and the mean years since menopause was 16.8. Baseline BMD at the lumbar spine and hip sites were similar between groups. Overall, 119 (25.4%) alendronic acid and 118 (25.2%) risedronic acid patients reported an upper gastrointestinal disorder at baseline. The most commonly reported medical history conditions were hypertension (32.2%), osteoarthritis (18.2%) and hypercholesterolaemia (15.1%). 265 patients (28.3%) reported use of an NSAID during the study (alendronic acid: n = 137, 29.3%; risedronic acid: n = 128, 27.4%).

Efficacy

Significant ($p \leq 0.001$) mean percentage increases from baseline in trochanter BMD at month 12 were observed in both treatment groups: 3.56% and 2.71% in the alendronic acid and risedronic acid groups, respectively (figure 2a). The difference between alendronic acid and risedronic acid in hip trochanter BMD at month 12 was 0.83% (95% CI 0.22, 1.45; $p = 0.008$). At month 12, significant ($p \leq 0.001$) mean percentage increases from baseline in lumbar spine, total hip and femoral neck BMD were observed in both treatment groups, with gains being significantly greater with alendronic acid than with risedronic acid (figure 2b–2d). The mean differences (95% CI) in BMD between alendronic acid and risedronic acid at month 12 were 0.75% (0.28, 1.23; $p = 0.002$) at the lumbar spine, 0.68% (0.30, 1.06; $p < 0.001$) at the total hip, and 0.56% (0.03, 1.09; $p = 0.039$) at the femoral neck. The greater increases in BMD with alendronic acid were demonstrated early, with statistically significant differ-

ences in trochanter and total hip being observed at 6 months. The treatment effects on BMD were consistent among the subgroup of patients who at baseline met the WHO definition of osteoporosis (BMD T-score ≤−2.5) or who had sustained a fracture of the wrist, hip or spine since the age of 45 years (data not shown).

A greater percentage of alendronic acid- than risedronic acid-treated patients achieved measured BMD increases (≥0%) at all sites at 12 months (figure 3). At month 12, for example, more patients in the alendronic acid group than in the risedronic acid group maintained or increased hip trochanter BMD (83.4% vs 76.7%, respectively; p = 0.013) and lumbar spine BMD (89.7% vs 85.4%, respectively; p = 0.064). Furthermore, significantly more alendronic acid than risedronic acid patients had measured gains in BMD ≥3% at the trochanter (57.5% vs 42.4%; p < 0.001), lumbar spine (68.3% vs 59.3%; p = 0.004), total hip (46.7% vs 31.0%; p < 0.001), and femoral neck (41.4% vs 32.4%; p = 0.005).

Significant percentage decreases (p ≤ 0.001) from baseline at month 12 were observed in both treatment groups for NTx, CTx, BSAP and P1NP. Alendronic acid produced significantly greater decreases (p < 0.001) from baseline than risedronic acid in all four of these biochemical markers of bone turnover at month 12 (figure 4a–4d), with differences being demonstrated at the earliest timepoint of 3 months (p < 0.001) and maintained throughout the duration of the study. The respective unadjusted mean decreases at month 12 for NTx, CTx, BSAP and P1NP were −58.1%, −79.9%, −44.6% and –67.5% for alendronic acid and –46.7%, –62.7%, –34.1% and –54.0% for risedronic acid.

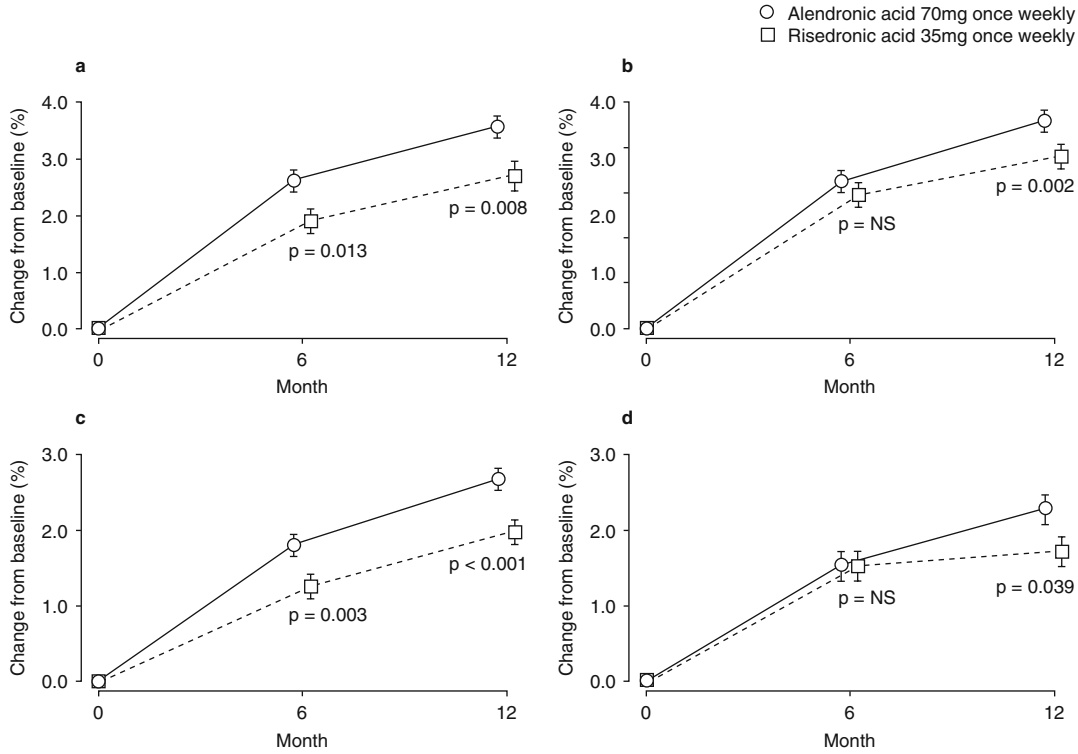

Fig. 2. Mean percentage changes in bone mineral density (BMD) from baseline (± SE) to month 12 (modified intention-to-treat approach). p-Values for between-treatment-group comparison: (**a**) hip trochanter BMD; (**b**) lumbar spine BMD; (**c**) total hip BMD; and (**d**) femoral neck BMD. **NS** = not significant.

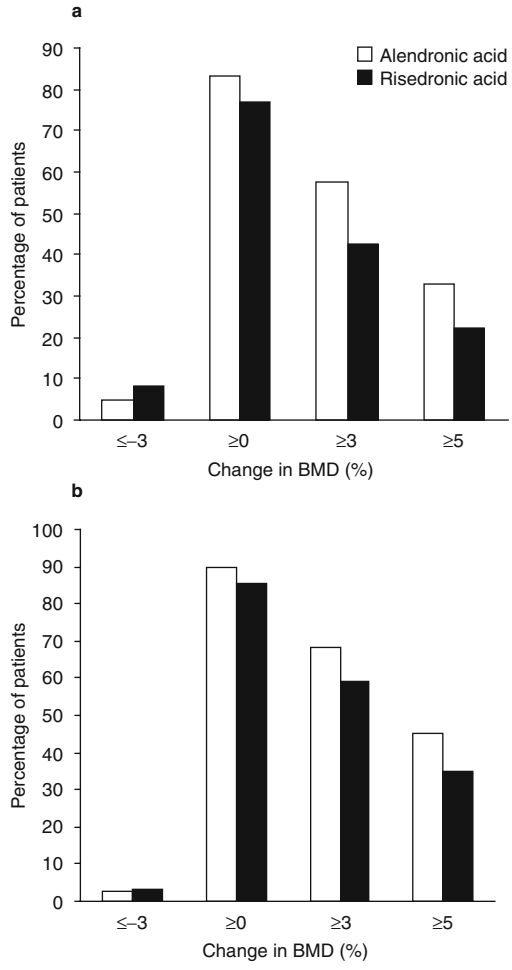

Fig. 3. Proportions of patients with bone mineral density (BMD) changes at 12 months that met prespecified cutoffs. (**a**) Hip trochanter. All comparisons of alendronic acid and risedronic acid were significant ($p = 0.042$ for ≤−3%, $p = 0.013$ for ≥0%, and $p \leq 0.001$ for ≥3% and ≥5%). (**b**) Lumbar spine. For comparisons of alendronic acid and risedronic acid, p = not significant for ≤−3%, $p = 0.064$ for ≥0%, and $p < 0.005$ for ≥3% and ≥5%.

Safety and Tolerability

Tolerability, including the proportion of patients discontinuing the study because of an AE, was similar between treatments (table II). There was no significant difference between groups in the proportion of patients reporting at least one clinical AE. The proportion of patients with a serious AE was significantly lower in the alendronic acid group compared with the risedronic acid group (5.1% vs 10.0%; $p = 0.006$). Six patients died during the study: two (0.4%) in the alendronic acid group and four (0.9%) in the risedronic acid group. The upper gastrointestinal AE profiles were generally similar between the treatment groups, with no significant differences observed between groups for the proportion of patients who had an upper gastrointestinal AE, a serious upper gastrointestinal AE, or who discontinued early because of an upper gastrointestinal AE (table II).

Clinical fractures were uncommon (incidence <4% in either treatment group). Fractures that occurred during the study were reported by investigators as AEs, whether or not they were associated with trauma and without requirements of radiographic confirmation or adjudication. Eighteen fractures (3.6% of patients) were reported in the alendronic acid group and 20 fractures (3.8% of patients) were reported in the risedronic acid group. There was no significant difference in the percentage of fracture AEs between treatment groups.

Discussion

The best method by which to evaluate the relative efficacy and tolerability of two therapies is direct (head-to-head) comparison. In the present head-to-head study, significantly greater increases in BMD at the hip trochanter, lumbar spine, total hip and femoral neck and greater reductions in biochemical markers of bone turnover were observed with once-weekly alendronic acid 70mg compared with once-weekly risedronic acid 35mg. Significant differences between treatments occurred early – within 3 months for changes in bone turnover markers and 6 months for changes in BMD at total hip and trochanter – and were maintained for the duration of the study. Alendronic acid also produced greater effects on BMD and turnover markers in the subgroup of patients who at baseline met the WHO definition of osteoporosis or who had sustained a wrist, hip or spine fracture after the age of 45 years – the type of patients most likely to be treated with bisphosphonates. Additionally, both alendronic acid and risedronic acid were generally well tolerated,

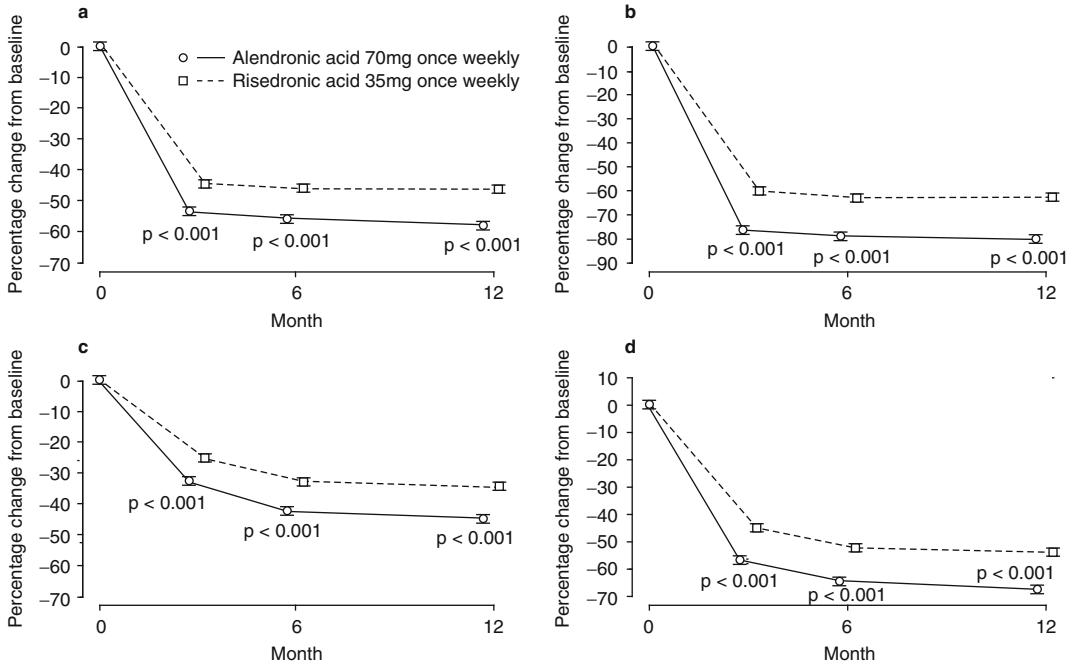

Fig. 4. Changes in biochemical markers expressed as mean percentage change from baseline (± SE) at 3, 6 and 12 months (per-protocol approach). p-Values for between-treatment-group comparison: (**a**) urinary N-telopeptide of type I human collagen corrected for creatinine (nmol bone collagen equivalents/mmol of creatinine); (**b**) serum C-telopeptide (ng/mL); (**c**) serum bone specific alkaline phosphatase (μg/L); and (**d**) serum N-terminal propeptide of type 1 procollagen (μg/L).

with a similar incidence of upper gastrointestinal AEs.

Fracture reduction is the primary goal of osteoporosis therapy. Unfortunately, head-to-head studies with fracture as an endpoint are not feasible because of the vast resources and number of patients that would be necessary to derive statistically meaningful results.[22] BMD and biochemical markers of bone turnover have been proposed as appropriate surrogate markers for fracture risk reduction.[10,27] Decreased BMD is an important risk factor for osteoporotic fracture, and hip BMD is a better predictor of subsequent hip fracture than BMD measurements in the lumbar spine or wrist.[28] In the present study, the hip trochanter was selected as the primary endpoint because of its high trabecular bone content,

Table II. Incidence of adverse experiences

Variable	Alendronic acid 70mg once weekly (n = 468) [n (%)]	Risedronic acid 35mg once weekly (n = 468) [n (%)]	p-Value
Adverse experiences			
Any	306 (65.4)	314 (67.1)	0.629
Serious	24 (5.1)	47 (10.0)	0.006
Causing discontinuation	20 (4.3)	28 (6.0)	0.300
Upper gastrointestinal			
Any	95 (20.3)	94 (20.1)	1.000
Serious	2 (0.4)	4 (0.9)	0.686
Causing discontinuation	8 (1.7)	11 (2.4)	0.644

which shows greater and more rapid responses to antiresorptive therapy.

As with BMD, larger changes in biochemical markers of bone turnover are also associated with larger reductions in fracture risk during antiresorptive therapy.[2-5,10,29] Although one study of risedronic acid[29] suggested a 'plateau' in this relationship for vertebral fractures, a larger study of alendronic acid demonstrated that the relationship persisted at all levels, and both studies reported a continuous, progressive relationship for nonvertebral fracture risk.[5] Bone turnover markers are reduced to within the premenopausal range during bisphosphonate treatment, and there is no evidence of 'oversuppression'.[30] If the results of these studies are accepted, the greater effects on BMD and turnover markers with alendronic acid than with risedronic acid observed in the current study predict greater reductions in the risk of both vertebral and nonvertebral fractures.

Another indicator of antiresorptive efficacy in this study was the percentage of patients with changes in hip trochanter or spine BMD ≥0% or ≥3%. In prior studies of alendronic acid and risedronic acid, patients with increases in BMD (≥0%) had lower fracture risk.[4,31] A BMD increase of 3% corresponds to the least significant change needed to be 95% confident that the improvement in BMD for an individual patient is real, when the test precision does not exceed 1%, as is typical for BMD.[32] BMD changes of ≥3% during antiresorptive therapy (including alendronic acid) have been associated with greater reductions in fracture risk in some but not all studies.[4,31,33] A greater proportion of patients increased BMD while taking alendronic acid compared with risedronic acid in the present study, indicating that patients treated with alendronic acid would be more likely to show an increase in BMD than would those given risedronic acid.

The tolerability profile of a therapeutic agent is a key consideration in determining its risk-benefit ratio and is strongly associated with long-term patient adherence. The present findings indicate that both overall tolerability and upper gastrointestinal tolerability were similar with alendronic acid and risedronic acid.

It is difficult to predict the magnitude of improvement in fracture risk based on the greater increases in BMD and reductions in bone turnover observed with alendronic acid relative to risedronic acid in the present study. Thus, it is important to consider all of the available data, including results from other direct head-to-head studies, meta-analyses, and individual randomised controlled trials. The present results are consistent with those of several recent studies. In a direct comparison trial of 549 postmenopausal women, once-weekly alendronic acid 70mg produced significantly greater increases in spine and hip BMD and reductions in biochemical markers of bone turnover than daily risedronic acid 5mg, and both agents were generally well tolerated.[25] In this earlier study, risedronic acid was administered 2 hours post-meal in accordance with the EU label at the time of the study; thus, it was not certain whether the observed differences between treatments may have been due to a greater antiresorptive effect of alendronic acid or decreased bioavailability of risedronic acid with post-meal administration.[25] A randomised clinical trial conducted in the US similar in design to the present study showed greater changes in BMD and greater decreases in bone turnover with once-weekly alendronic acid 70mg compared with once-weekly risedronic acid 35mg when both drugs were administered using standard morning oral doses.[26] The current study was somewhat more ethnically diverse than the US study, with ~79% versus ~95% Caucasian participants, which may make the results more generalisable. Nevertheless, mean BMD levels in the US study were similar to those in the current study. The consistent results demonstrated in three studies[25,26] (including the current study) provide greater assurance of the reliability of the conclusions, reducing the chance of spurious findings. In addition, the results of meta-analyses of therapies for osteoporosis reporting larger increases in BMD and greater fracture risk reductions for alendronic acid versus risedronic acid are fully consistent with the present findings.[21]

Conclusions

This 12-month, randomised, international, head-to-head trial of the once-weekly oral regimens of alendronic acid and risedronic acid demonstrated that alendronic acid produced greater increases in BMD at all sites and reductions in all markers of bone turnover than risedronic acid for the treatment of postmenopausal osteoporosis. The efficacy differences between the two agents were observed early (within months) and persisted over the entire 12-month study. These results are consistent with those of previously reported clinical studies, head-to-head trials and meta-analyses. Both alendronic acid and risedronic acid were well tolerated with no significant difference in upper gastrointestinal adverse experiences. Clinicians should consider these results when making treatment decisions for postmenopausal women with osteoporosis.

Acknowledgements

This clinical trial was funded by Merck & Co., Inc.; no funding was received for manuscript development. D.M. Reid, D. Hosking, D. Kendler, M.L. Brandi and J.D. Wark have served as paid consultants and/or speakers for Merck & Co., Inc. M.L. Brandi has served as a paid speaker for Procter and Gamble Pharmaceuticals. K. Gaines, N. Verbruggen and M.E. Melton are employees of Merck & Co., Inc. and potentially own stock and/or hold stock options in the company.

The authors would like to recognise the valuable contributions of Christine Sisk to the writing of earlier versions of this manuscript and the expert review and comments to the manuscript provided by Philip Ross, PhD, both of Merck. The authors would also like to recognise the efforts of the study staff at the investigative sites, including the following lead investigators: *Australia:* J. Eden, J. Graham, M. Hooper, E. Seeman, J. Wark, C. White; *Belgium:* S. Boonen, Y. Boutsen, J. Kaufman, M. Malaise, J.-Y. Reginster. *Brazil:* J.F.M. Neto, J.R. Provenza; *Canada:* J. Brown, D. Kendler, A. Khan; Chile: A. Brizzolara, L. Villanueva; *Costa Rica:* A. Cob, W. Rios; *Dominican Republic:* J.V. de Camps, C. Velazco; *Ecuador:* C. Bracho; *Finland:* M. Valimaki; *France:* C.-L. Benhamou, F. Blotman, P. Delmas, L. Euller-Ziegler, P. Fardellone, Y. Maugars, C. Ribot, T. Thomas, G. Weryha; Greece: A. Avramides; Hungary: L. Koranyi, P. Lakatos; Italy: M.L. Brandi, C.E. Fiore, Q. Mela, R. Nuti; *Jordan:* B. Masri; *Latvia:* A. Lejnieks, I. Rasa; *Lebanon:* H. Awada, G. Maalouf, C. Saab; *Lithuania:* V. Alekna, M. Tamulaitiene, L. Valius; *Malaysia:* S.P. Chan; *Peru:* L. Danckers, R. Olavide, R. Salinas; *Poland:* R. Lorenc, S. Mackiewicz, T. Pertyński; *Portugal:* A. Faustino, J.M. Gomes; *Slovenia:* A. Kocijančič; *Spain:* J.J. Gomez-Reino, C. Lozano-Tonkin, J.L. Perez-Castrillon, M. Rodriguez-Perez, J. Roman-Ivorra; Taiwan: J.-F. Chen, S.-M. Hou; *Thailand:* B. Ongphiphadhanakul, K. Wilawan; *UK:* M. Davie, D. Hosking, R. Keen, D. Reid, O. Sahota, P. Selby, M. Stone; *Venezuela:* T. López.

[ClinicalTrials.gov registry number: 00092040]

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