ORIGINAL ARTICLE

Early response to alendronate after treatment with etidronate in postmenopausal women with osteoporosis

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Abstract. The purpose of the present study was to examine the early response of lumbar bone mineral density (BMD), bone resorption, and back pain to alendronate after treatment with cyclical etidronate in postmenopausal women with osteoporosis. Forty postmenopausal women with osteoporosis, 60–83 years of age, without any vertebral fractures in the lumbar spine, were randomly divided into two groups with 20 patients in each group: 18 months of cyclical etidronate (200 mg daily for 2 weeks every 3 months) group and 12 months of cyclical etidronate followed by 6 months of alendronate (5 mg daily) group. BMD of the lumbar spine (L1–L4) measured by DXA, urinary cross-linked N-terminal telopeptides of type I collagen (NTX) level measured by enzyme-linked immunosorbent assay, and back pain evaluated by face scale score were assessed at baseline and every 6 months. There were no significant differences in baseline characteristics including age, body mass index, years since menopause, lumbar BMD, urinary NTX level, and face scale score between the two groups. Cyclical etidronate significantly reduced urinary NTx level and face scale score over 12 months, but did not significantly increase lumbar BMD. After 12 months of treatment, the switch to alendronate significantly reduced urinary NTX level and face scale score, and significantly increased lumbar BMD, while continued cyclical etidronate did not significantly alter these parameters. These results suggest that switching to alendronate after treatment with cyclical etidronate produces a greater response of lumbar BMD, bone resorption, and back pain than continued cyclical etidronate in postmenopausal women with osteoporosis. (Keio J Med 52 (2): 113–119, June 2003)

Key words: postmenopausal osteoporosis, etidronate, alendronate, bone mineral density (BMD), urinary N-terminal telopeptides of type I collagen (NTX)

Introduction

Osteoporosis is a common health problem in postmenopausal women. Hormone replacement therapy is the treatment of choice in prevention of bone loss in early postmenopausal women, while bisphosphonates are useful agents to increase bone mineral density (BMD) and subsequently prevent osteoporotic fractures in elderly women. Bisphosphonates such as etidronate and alendronate are widely used for osteoporosis treatment in Japan. Both agents are generally accepted as a safe, effective, and well-tolerated treatment for postmenopausal osteoporosis. These bisphosphonates may inhibit osteoclast-mediated bone resorption, and loss of osteoclast function and apoptosis are probably the consequence of loss of function of one or more of important signaling proteins. Etidronate can be metabolically incorporated into nonhydrolyzable analogs of ATP, and intracellular accumulation of these metabolites is likely to inhibit osteoclast function.[1] A nitrogen-containing bisphosphonate like alendronate is not metabolized but can inhibit enzymes of the mevalonate pathway, thereby preventing the biosynthesis of isoprenoid compounds that are essential for the post-translational modification of small GTPases.[1] Thus, the mechanism for inhibition of bone resorption may differ between etidronate and alendronate.

Histomorphometric studies have confirmed that both

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agents bring about benefit in osteoporotic patients without inhibition of skeletal mineralization.[2,3] Cyclical etidronate decreases bone resorption, increasing lumbar BMD and reducing the incidence of vertebral fractures.[4–8] On the other hand, alendronate increases BMD of the lumbar spine and femoral neck and reduces the incidence of vertebral and femoral neck fractures.[9–11] Alendronate seems to have a greater effect on osteoporosis than etidronate. Available evidence also suggests that alendronate is effective in patients who do not respond to etidronate.[12,13] In particular, Fairney *et al.*[12] provided evidence indicating that postmenopausal women with osteoporosis who did not respond to etidronate only with regard to an increase in lumbar BMD did so following alendronate. However, the efficacy of alendronate after cyclical etidronate not only for lumbar BMD but also for bone resorption and spinal osteoporosis-related back pain in patients with osteoporosis, including responders to cyclical etidronate, has not necessarily been established. The purpose of the present study was to examine the early response of lumbar BMD, bone resorption, and back pain to alendronate after treatment with cyclical etidronate in postmenopausal women with osteoporosis.

Subjects and Methods

Subjects

Forty postmenopausal women, 60–83 years of age, without any vertebral fractures in the lumbar spine, were recruited at our hospital between January and March 2001. All of them were diagnosed as having osteoporosis based on the Japanese criteria.[14,15] They were randomly divided into two groups with 20 patients in each group: 18 months of cyclical etidronate (200 mg daily for 2 weeks every 3 months) group (E group) and 12 months of cyclical etidronate followed by 6 months of alendronate (5 mg daily) group (EA group). In the EA group, in particular, the switching to alendronate treatment after cyclical etidronate treatment was strictly performed without crossover of both treatments. Preliminary screening included medical history, physical examination, plain X-ray examination of the thoracic and lumbar spine, lumbar BMD measurement, blood and urine biochemical tests, and a questionnaire to evaluate back pain. After the start of treatment, lumbar BMD, urinary biochemical parameters, and back pain were assessed every 6 months, and plain X-ray of the thoracic and lumbar spine was assessed at the end of the 18 months of treatment. Assessment of vertebral fractures on plain X-ray films and lumbar BMD measurement were performed as described below. Serum calcium and phosphorus levels were measured with standard laboratory techniques. The urinary level of cross-linked N-terminal telopeptides of type I collagen (NTX) was measured by an enzyme-linked immunosorbent assay. None of the subjects suffered from any metabolic bone disease, and none had a history of hormone (estrogen) replacement therapy or had ever taken medication that affects bone metabolism prior to the present study. All subjects were instructed to take 800 mg of calcium daily through their food intake during the study. Informed consent was obtained from each of the participants, and all participants could complete the present trial.

Assessment of vertebral fractures

Plain lateral X-ray films of the thoracic and lumbar spine were obtained to find evidence of vertebral fractures. Vertebral fracture was defined according to vertebral height obtained from lateral X-ray films based on the Japanese criteria.[14,15] Briefly, vertebral height was measured at the anterior (A), center (C), and posterior (P) parts of the vertebral body, and the presence of vertebral fracture was confirmed when (1) more than a 20% reduction of vertebral height (A, C, and P) compared with the neighboring vertebrae was observed; (2) C/A or C/P was less than 0.8; or (3) A/P was less than 0.75. Assessment of vertebral fractures in the T4-L4 spine was performed in the present study.

Measurement of lumbar BMD

BMD of the lumbar spine (L1–L4) in the anteroposterior view was measured by dual energy X-ray absorptiometry (DXA) using a Hologic QDR 1500W instrument (Bedford, MA, USA). The coefficient of variation (100 × standard deviation/mean) of five measurements each time with repositioning within 72 hours was less than 1.2% in three persons.

Evaluation of back pain

Back pain was evaluated quantitatively by assessing the mood of patients according to the face scale. The face scale contains ten drawings of a single face, arranged in serial order by rows, with each face depicting a slightly different mood. Subtle changes in the eyes, eyebrows, and mouth are used to represent slightly different levels of mood. They are arranged in decreasing order of mood and numbered from 1–10, with 1 representing the most positive mood and 10 representing the most negative mood. As the examiner pointed to the faces, the following instructions were given to each patient: ''The faces below go from no pain at the top to severe pain at the bottom. Point to the face that best shows your current level of back pain.'' Thus, facial expression is used as an indicator of back pain. The validity and reliability of the face scale have been dem-

onstrated,[16] although pain is a subjective symptom that is relatively difficult to evaluate.

Statistical analysis

Data are expressed as mean ± standard deviation (SD). Data comparisons between the two groups were performed by unpaired t-test. The significance of longitudinal changes in lumbar BMD, urinary NTx level, face scale score, and serum calcium and phosphorus levels was determined by one-way analysis of variance (ANOVA) with repeated measurements. The correlation among baseline lumbar BMD, urinary NTX level, and face scale score was examined by single regression analysis. All statistical analyses were performed using the Stat View-J5.0 program on a Macintosh computer. A significance level of $P < 0.05$ was used for all comparisons.

Results

Characteristics of subjects

Table 1 shows the baseline characteristics of the study subjects. The mean age of the subjects was 71.3 years in the E group and 70.9 years in the EA group. There were no significant differences in mean age, height, body weight, body mass index, years since menopause, and serum calcium and phosphorus levels between the two groups. Serum calcium and phosphorus levels were within the normal range in all subjects. The mean lumbar BMD was 0.607 g/cm^2 (T score: 59.7%) in the E group and 0.605 g/cm^2 (T score: 59.5%) in the EA group. The respective mean urinary NTX level was 64.7 and 69.7 nmol BCE/mmol Cr; the respective mean face scale score was 5.1 and 4.8; and the respective mean number of prevalent thoracic vertebral fractures per patient was 1.55 and 1.45. There were no significant differences in baseline lumbar BMD (T score), urinary NTX level, face scale score, and number of prevalent thoracic vertebral fractures between the two groups.

Table 1 Characteristics of Study Subjects

	E group	EA group
Age (years)	71.3 ± 6.0	70.9 ± 6.2
Height (m)	1.49 ± 0.06	1.47 ± 0.05
Body weight (kg)	45.8 ± 6.0	47.5 ± 8.1
BMI (kg/m^2)	20.6 ± 2.7	21.8 ± 3.3
YSM	21.3 ± 6.0	21.0 ± 6.7
Lumbar BMD (g/cm^2)	0.607 ± 0.099	0.605 ± 0.096
T score of lumbar BMD (%)	59.7 ± 9.7	59.5 ± 9.5
Serum calcium (mg/dl)	9.5 ± 0.4	9.5 ± 0.3
Serum phosphorus (mg/dl)	3.2 ± 0.4	3.4 ± 0.4
Urinary NTX (nmol BCE/mmol Cr)	64.7 ± 24.7	69.7 ± 21.3
Face scale score	5.1 ± 1.1	4.8 ± 1.0
Number of vertebral fractures per patient	1.55 ± 1.91	1.45 ± 1.85

Data are expressed as means ± SD. Data comparison was performed by unpaired t-test. There were no significant difference in any characteristics of the study subjects between the two groups. BMI: body mass index, YSM: years since menopause, BMD: bone mineral density, NTX: N-terminal telopeptides of type I collagen.

Changes in lumbar BMD, urinary NTX level, face scale score, and serum calcium and phosphorus levels

Table 2 and Fig. 1 show the longitudinal percent changes in lumbar BMD, urinary NTX level, face scale score, and serum calcium and phosphorus levels. In the E group, the mean percent changes in lumbar BMD were +1.88% at 6 months, +2.37% at 12 months, and +3.22% at 18 months compared with baseline. The corresponding changes in urinary NTX level were −16.5%, −39.6%, and −43.4%, and those in face scale score were −23.3%, −26.9%, and −25.9%. In the EA group, the mean percent changes in lumbar BMD were +1.90% at 6 months, +3.95% at 12 months, and +7.04% at 18 months compared with baseline. The corresponding changes in urinary NTX level were −19.0%, −51.2%, and −63.4%, and those in face scale score were −22.5%, −27.6%, and −32.9%. In both groups, urinary NTX level and face scale score were significantly decreased at 12 months, with no significant increase in lumbar BMD. After 12 months of treatment, in the E group, no significant changes in lumbar BMD, urinary NTX level, and face scale score were observed, while in the EA group, urinary NTX level and face scale score significantly decreased and lumbar BMD significantly increased. In both groups, no significant changes in serum calcium and phosphorus levels were observed during the 18 months of treatment.

Correlation among baseline lumbar BMD, urinary NTX level, and face scale score

A significant positive correlation was found between baseline urinary NTX level and face scale score in all patients ($r = 0.050$, $P < 0.05$), while no significant correlation was found between baseline lumbar BMD and urinary NTX level or face scale score ($r = -0.076$ and $r = -0.048$, respectively).

Analysis of response to alendronate

Table 3 shows the relationships of the urinary NTX level reduction after 12 months of cyclical etidronate treatment with the response of urinary NTX level, lumbar BMD, and face scale score to the switch to alendro-

Table 2 Changes in Lumbar BMD, Urinary NTX Level, Face Scale Score, and Serum Calcium and Phosphorus Levels

	Baseline	Month 6	Month 12	Month 18	Baseline–Month 12 (One-way ANOVA)	Month 12–18 (One-way ANOVA)	Baseline–Month 18 (One-way ANOVA)
Lumbar BMD (g/cm^2)							
E group	0.607 ± 0.099	0.619 ± 0.104	0.622 ± 0.106	0.628 ± 0.114	NS	NS	NS
(% change)		(1.88 ± 7.32)	(2.37 ± 7.55)	(3.22 ± 8.93)		(0.77 ± 3.81)	
EA group	0.605 ± 0.096	0.615 ± 0.094	0.628 ± 0.099	0.645 ± 0.088	NS	$p < 0.05$	$p < 0.001$
(% change)		(1.90 ± 6.21)	(3.95 ± 7.66)	(7.04 ± 7.84)		(3.10 ± 5.40)	
Urinary NTX (nmol BCE/mmol Cr)							
E group	64.7 ± 24.7	51.1 ± 21.6	36.2 ± 13.9	32.9 ± 13.8	$p < 0.001$	NS	$p < 0.001$
(% change)		(−16.5 ± 30.4)	(−39.6 ± 27.3)	(−43.4 ± 27.0)		(−5.05 ± 31.14)	
EA group	69.7 ± 21.3	53.3 ± 21.6	33.0 ± 12.9	24.7 ± 9.7	$p < 0.001$	$p < 0.01$	$p < 0.001$
(% change)		(−19.0 ± 35.6)	(−51.2 ± 15.4)	(−63.4 ± 13.8)		(−21.99 ± 26.66)	
Face scale score							
E group	5.1 ± 1.1	3.8 ± 1.0	3.6 ± 0.9	3.7 ± 0.9	$p < 0.001$	NS	$p < 0.001$
(% change)		(−23.3 ± 20.6)	(−26.9 ± 19.1)	(−25.9 ± 19.4)		(3.42 ± 22.06)	
EA group	4.8 ± 1.0	3.7 ± 0.8	3.4 ± 0.9	3.1 ± 0.9	$p < 0.001$	$p < 0.05$	$p < 0.001$
(% change)		(−22.5 ± 18.0)	(−27.6 ± 18.5)	(−32.9 ± 21.1)		(−7.00 ± 20.54)	
Serum calcium (mg/dl)							
E group	9.52 ± 0.36		9.56 ± 0.43	9.60 ± 0.53	NS	NS	NS
(% change)			(0.47 ± 4.17)	(0.87 ± 4.80)		(0.41 ± 2.91)	
EA group	9.52 ± 0.027		9.44 ± 0.36	9.73 ± 0.81	NS	NS	NS
(% change)			(−0.73 ± 4.16)	(2.20 ± 7.91)		(3.02 ± 7.49)	
Serum phosphorus (mg/dl)							
E group	3.23 ± 0.40		3.23 ± 0.35	3.12 ± 0.40	NS	NS	NS
(% change)			(0.45 ± 11.96)	(−2.51 ± 15.03)		(−2.78 ± 10.21)	
EA group	3.43 ± 0.35		3.13 ± 0.40	3.23 ± 0.41	NS	NS	NS
(% change)			(−8.01 ± 13.97)	(−5.31 ± 13.23)		(3.90 ± 14.18)	

Data are expressed as means ± SD. The significance of longitudinal changes in lumbar BMD, urinary NTX levels, face scale score, and serum calcium and phosphorus levels was determined by one-way analysis of variance (ANOVA) with repeated measurements. BMD: bone mineral density, NTX: N-terminal telopeptides of type I collagen. NS: not significant.

nate in EA group. In particular, patients with a <50% reduction in urinary NTX level following 12 months of cyclical etidronate treatment (n = 10) had a significant response of lumbar BMD, urinary NTX level, and face scale score to the switch to alendronate, but not those with a ≧50% reduction (n = 10).

Incidence of vertebral fractures

At the end of 18 months of treatment, plain X-ray examination of the thoracic and lumbar spine revealed no evidence of incident thoracic vertebral fracture in any patient. During the 18 months of treatment, non-vertebral osteoporotic fractures did not occur in the hip, wrist, or shoulder in any patient.

Adverse events

No adverse events such as gastrointestinal, skin, nervous system, musculoskeletal, and urinary tract-related symptoms were observed in any patient.

Discussion

Low calcium intake is one of the major reasons for the increase in the population with osteoporosis. Therefore, calcium supplementation could be a reasonable and effective treatment for osteoporosis. It is suggested that calcium supplementation may have little effect in preventing bone loss in women early after menopause, but may have the potential to bring about a positive effect on bone mass in women late after menopause, who are elderly, have a low-calcium diet, and/or have apparent evidence of osteoporosis.[17,18] In the present study, all patients were late menopausal women and had apparent osteoporosis. They were instructed to take at least 800 mg of calcium daily through their food intake.

The benefit of cyclical etidronate may lie in the fact that its treatment results in positive effects on the skeleton with only 2 weeks of administration every 3 months. Therefore, one can say that cyclical etidronate may have a smaller incidence of gastrointestinal tract

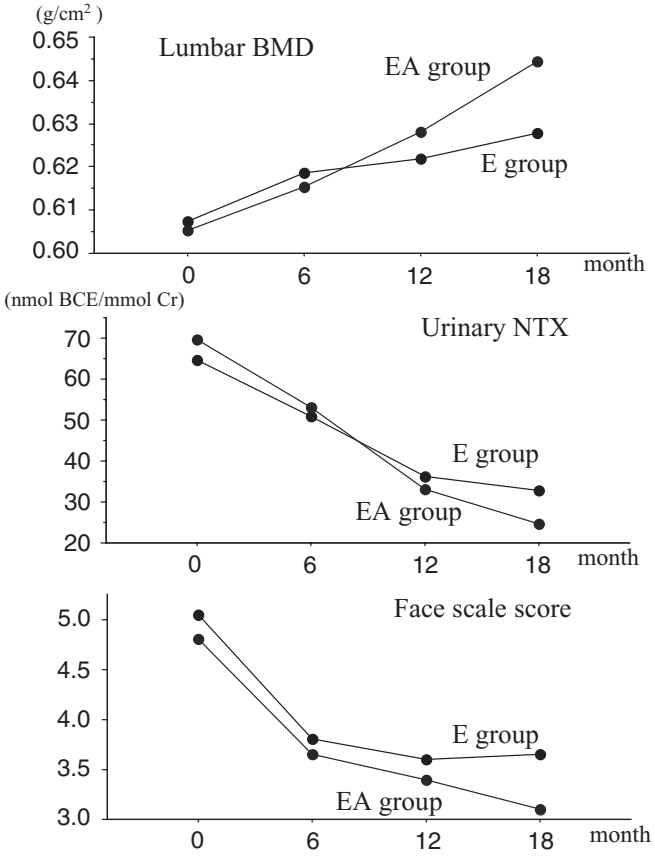

Fig. 1 Changes in mean lumbar BMD, urinary NTX level, and face scale score. BMD: bone mineral density, NTX: N-terminal telopeptides of type I collagen.

Table 3 Percent Changes in Lumbar BMD, Urinary NTX Level, and Face Scale Score after 6 Months of Alendronate

Reduction in urinary NTX level after 12 months of etidronate	Percent change by 6 months of alendronate		
	Lumbar BMD (%)	Urinary NTX (%)	Face scale score (%)
<50% (n = 10)	+4.26 ± 7.77	−30.6 ± 16.4	−12.8 ± 24.2
One-way ANOVA	$p < 0.01$	$p < 0.01$	$p < 0.05$
≧50% (n = 10)	+2.36 ± 2.21	−20.7 ± 24.1	−2.5 ± 17.6
One-way ANOVA	NS	NS	NS

Data are expressed as means ± SD. The significance of longitudinal changes in lumbar BMD, urinary NTX levels, and face scale score was determined by one-way analysis of variance (ANOVA) with repeated measurements. BMD: bone mineral density, NTX: N-terminal telopeptides of type I collagen. NS: not significant.

events and subsequently greater compliance than alendronate. Based on this opinion, some doctors may prescribe at first etidronate for postmenopausal women with osteoporosis. The present study showed that cyclical etidronate reduced the urinary NTX level over 12 months, but did not increase lumbar BMD. Cyclical etidronate at 200 mg daily for 2 weeks followed by 10 weeks without drug has been shown to increase lumbar BMD in Japanese patients with osteoporosis by 2.4% after 2 years.[4] The non-significant increase in lumbar BMD (2.37% after 1 year) in the present study may be primarily due to the small sample size.

The correlation between face scale score and urinary NTX level at baseline was quite weak. However, cyclical etidronate reduced back pain as well as urinary NTX level. The effect of etidronate on back pain in patients with osteoporosis has rarely been reported, and the mechanisms by which osteoporosis causes back pain and etidronate improves it remain uncertain. Recently, the efficacy of bisphosphonates for bone pain through suppression of bone resorption has been demonstrated in patients with bone resorption-related diseases such as rehabilitating elderly patients suffering from chronic and refractory back pain due to osteoporotic vertebral fractures,[19] patients with skeletal metastases,[20–22] and patients with Paget's disease of bone.[23] This line of evidence suggests that bone pain may be linked to increased bone resorption, and that suppressed bone resorption may partially contribute to the relief of bone pain. We surmise that microfractures caused by increased bone resorption in the trabeculae of the spine can cause back (bone) pain, and that suppression of bone resorption and subsequent prevention and healing of microfractures in the trabeculae of the spine may play a role in the reduction in back (bone) pain. Relief of back pain by intervention is important in the elderly to improve their activity of daily living and subsequent quality of life. Nevitt *et al.*[24] reported that long-term alendronate treatment significantly lowered the likelihood of patients having days of bed rest and limited activity due to back pain in elderly osteoporotic women, suggesting that alendronate treatment in elderly osteoporotic patients is efficacious not only for preventing incident vertebral fractures by suppressing bone resorption, but also for reducing the burden of limitation of activity and disability necessitating bed rest caused by back pain.

Alendronate (5 mg daily) has been shown to suppress bone resorption and increase lumbar BMD by 6.21% after one year in Japanese patients with osteoporosis.[25] The anti-resorptive effects of alendronate on bone in patients with osteoporosis are greater than those of cyclical etidronate (200 mg for 2 weeks every 3 months).[4] In the present study, the early response of lumbar BMD, urinary NTX level, and back pain to a switch to alendronate after cyclical etidronate treatment was significant in postmenopausal women with osteoporosis. The reason for this greater response remains uncertain. It has been demonstrated that a daily dose of 10 mg was more effective than one of 5 mg

for suppressing bone resorption and increasing lumbar BMD in patients with osteoporosis.[11] This result suggests that the more strongly bone resorption is suppressed in osteoporosis, the greater the increase in BMD is. Furthermore, histomorphometric studies have demonstrated that bisphosphonates such as etidronate and alendronate reduce the remodeling space by decreasing the activation frequency in trabecular bone in postmenopausal women with osteoporosis.[2,3] Therefore, we surmise that because suppression of bone resorption by etidronate was relatively mild, the remodeling spaces were still large enough to be reduced by the more potent bisphosphonate alendronate, and that this may be one of the reasons for the greater response to alendronate.

In particular, patients with a <50% reduction in urinary NTX level after 12 months of cyclical etidronate had a greater response of lumbar BMD, urinary NTX level, and face scale score to alendronate than those with a ≧50% reduction. This result indicates that alendronate may show a better response in patients who had a poorer response to cyclical etidronate, consistent with the report by Fairney *et al*.[12] indicating that alendronate was effective for patients who did not respond to etidronate. Conversely, the poor response of lumbar BMD, urinary NTX level, and face scale score to alendronate in patients with a ≧50% reduction in urinary NTX level after 12 months of cyclical etidonate may be due to the markedly reduced remodeling space that would be filled by alendronate.

Alendronate also promoted improvement of back pain as well as a reduction in urinary NTX level. This result supports our view that back pain may be linked to increased bone resorption in osteoporosis, and that suppressed bone resorption may partially contribute to the relief of back pain.

A limitation of the present study is that there were no placebo controls. First, it remains uncertain whether the change in lumbar BMD by etidronate is significant compared with placebo controls. Second, because pain is a subjective symptom, whether the reduction in back pain by etidronate or alendronate reflects a true drug effect is not known. Third, because the pain caused by vertebral microfractures is usually transient, resolving within a few weeks to a few months, whether the longitudinal decline in face scale score by etidronate reflects a true drug effect is also not known. Therefore, a double-blind placebo-controlled study is needed to confirm the efficacy of etidronate for postmenopausal osteoporosis.

In conclusion, cyclical etidronate reduced the urinary NTX level and improved back pain over 12–18 months in postmenopausal women with osteoporosis, but did not increase lumbar BMD. After 12 months of treatment, a switch to alendronate significantly reduced the urinary NTX level and face scale score, and significantly increased lumbar BMD, while continued cyclical etidronate did not significantly alter these parameters. These results suggest that the switch to alendronate after treatment with cyclical etidronate produces a greater response of lumbar BMD, bone resorption, and back pain than continued cyclical etidronate in postmenopausal women with osteoporosis. Because the present study did not contain placebo controls, further study will be needed to confirm our results.

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