Factors Affecting Discontinuation of Alendronate Treatment in Postmenopausal Japanese Women With Osteoporosis

Jun Iwamoto[1]*, Atsushi Miyata[2], Yoshihiro Sato[3], Tsuyoshi Takeda[1], Hideo Matsumoto[1]

[1]*Institute for Integrated Sports Medicine, Keio University School of Medicine,* [2]*Department of Internal Medicine, Yahata Clinic, Tokyo, and* [3]*Department of Neurology, Mitate Hospital, Fukuoka, Japan.*

Background: The main challenge to the long-term treatment of osteoporosis with bisphosphonates has been patient adherence. The purposes of this cohort study were to investigate the 3-year outcome of alendronate treatment in postmenopausal Japanese women with osteoporosis and to identify factors that contributed to the discontinuation of alendronate treatment.

Methods: A total of 72 postmenopausal Japanese women with osteoporosis and aged from 58 to 85 years were treated with alendronate in a 3-year trial. Metacarpal bone mineral density, serum alkaline phosphatase, and urinary cross-linked N-terminal telopeptides of type I collagen were monitored, and factors contributing to the discontinuation of alendronate treatment were determined.

Results: Fourteen patients dropped out of the trial. The reasons for dropout were side effects (diarrhea [$n=1$], gastric symptoms [$n=9$], and inflammation of the mouth [$n=1$]) or non-compliance ($n=3$). Logistic regression analysis showed that the number of prevalent vertebral fractures was a significant factor affecting the discontinuation of alendronate treatment for the reasons listed above. In 58 patients who continued the 3-year treatment, urinary cross-linked N-terminal telopeptides of type I collagen level was reduced by 44.1% at 3 months and serum alkaline phosphatase level was decreased by 11.6%, 11.8%, and 12.5% at 1, 2, and 3 years, respectively. However, metacarpal bone mineral density did not change significantly.

Conclusion: Alendronate treatment decreased urinary cross-linked N-terminal telopeptides of type I collagen and serum alkaline phosphatase levels, and maintained metacarpal bone mineral density in postmenopausal Japanese women with osteoporosis. The patients adhered well to alendronate treatment in our clinic. The number of prevalent vertebral fractures was an important factor affecting the discontinuation of alendronate treatment due to side effects and non-compliance. [*J Chin Med Assoc* 2009;72(12):619–624]

Key Words: alendronate, bone mineral density, cross-linked N-terminal telopeptides of type I collagen, metacarpus, osteoporosis

Introduction

The efficacy of bisphosphonates such as alendronate in the treatment of osteoporosis in postmenopausal women has been established. According to global data, alendronate treatment increases lumbar and hip bone mineral density (BMD) and decreases the incidence of vertebral and hip fractures.[1,2] Japanese data show that alendronate treatment increases lumbar and hip BMD and prevents vertebral fractures.[3–6]

To diagnose and treat osteoporosis, an assessment of BMD is required. Dual energy X-ray absorptiometry is utilized to measure lumbar, femoral neck, and forearm BMD, and computed X-ray densitometry is used to measure metacarpal BMD. Because dual energy X-ray absorptiometry machines are very expensive, they are not always available. Therefore, many Japanese hospitals and clinics measure metacarpal BMD using computed X-ray densitometry to diagnose osteoporosis and to monitor the efficacy of medication on

*Correspondence to: Dr Jun Iwamoto, Institute for Integrated Sports Medicine, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan.
E-mail: jiwamoto@sc.itc.keio.ac.jp • Received: March 10, 2009 • Accepted: October 29, 2009

osteoporosis treatment. The long-term adherence of patients has been the main challenge to effective treatment using bisphosphonates. However, there are few reports of the long-term effects of alendronate on metacarpal BMD, and furthermore, the factors affecting the adherence of patients to alendronate treatment have not been established in postmenopausal Japanese women with osteoporosis. The purposes of this cohort study were to investigate the 3-year outcome of alendronate treatment in postmenopausal Japanese women with osteoporosis and to identify the factors that contribute to the discontinuation of alendronate treatment.

Methods

Subjects

Seventy-two postmenopausal Japanese women with osteoporosis,[7,8] aged 57–85 years, were recruited at Yahata Clinic (Tokyo, Japan) from October 2001 to September 2002. Using the Japanese criteria for osteoporosis in women,[7,8] patients whose BMD was either <70% of the young adult mean or 70–80% of the young adult mean together with a history of osteoporotic fractures were diagnosed as having osteoporosis. Inclusion criteria were postmenopausal women with osteoporosis with or without a history of osteoporotic fractures. Exclusion criteria were histories of reflux esophagitis, gastric or duodenal ulcer, gastrectomy, or bone diseases including primary hyperparathyroidism, hyperthyroidism, Cushing's syndrome, multiple myeloma, rheumatoid arthritis, and osteogenesis imperfecta. Women who had ever taken medication known to affect bone metabolism were also excluded. All subjects participated in a 3-year trial of alendronate treatment (5 mg daily). This dose is recognized as effective for Japanese patients with osteoporosis.[3–6] All subjects were given a pamphlet instructing them to take 800 mg of calcium daily through food intake. Table 1 shows the characteristics of the study subjects. Informed consent was obtained from all subjects.

Subjects were monitored and followed-up with pre-and post-treatment examinations that included a medical history, physical examination, radiographic examination of the thoracic and lumbar spine, metacarpal BMD measurement, and blood and urine biochemical tests. Assessment of vertebral fractures on radiographs and metacarpal BMD measurement were performed as described below. Metacarpal BMD measurement was assessed at baseline and once every year after that. Serum calcium, phosphorus, and alkaline phosphatase (ALP) levels were measured with standard laboratory techniques at baseline and once every year after that. Urinary cross-linked N-terminal telopeptides of type I collagen (NTX) level was measured by enzyme-linked immunosorbent assay at baseline and then only once, 3 months after the start of treatment. A general practitioner (GP) at Yahata Clinic carried out the treatments. All participants met the GP at least once a month during the 3-year treatment period as long as they continued alendronate treatment. The ethics committee of Yahata Clinic approved the protocol for this study.

Table 1. Characteristics of all 72 study subjects*

Age (yr)	73.4 ± 5.8 (58–85)
Height (m)	1.47 ± 0.06 (1.34–1.60)
Body weight (kg)	47.5 ± 7.0 (34–65)
Body mass index (kg/m^2)	21.8 ± 2.4 (16.9–27.4)
Years since menopause	22.7 ± 5.6 (10–36)
BMD (mm Al)	1.88 ± 0.24 (1.07–2.19)
BMD % of YAM (%)	69 ± 9 (39–79)
Serum calcium (mg/dL)	8.9 ± 0.3 (8.3–9.8)
Serum phosphorus (mg/dL)	3.6 ± 0.6 (2.4–5.6)
Serum ALP (IU/L)	234 ± 94 (98–482)
Urinary NTX (nmol BCE/mmol Cr)	69.0 ± 31.7 (35.0–160.3)
Vertebral fractures (*n*)	2.3 ± 2.3 (0–8)

**Data are presented as mean ± standard deviation (range). BMD = bone mineral density; mm Al = aluminum equivalent; YAM = young adult mean; ALP = alkaline phosphatase; NTX = cross-linked N-terminal telopeptides of type I collagen; nmol BCE/mmol Cr = bone collagen equivalent per mmol of creatinine.*

Assessment of vertebral fractures

Radiographs of the thoracic and lumbar spine were taken to find evidence for vertebral fractures. Vertebral fracture was defined according to the vertebral height obtained from lateral X-ray films based on the Japanese criteria.[7,8] Briefly, vertebral height was measured at the anterior (A), central (C), and posterior (P) parts of the vertebral body, and the presence of a vertebral fracture was confirmed when: (1) there was more than 20% reduction of vertebral height (A, C, and P) compared with the neighboring vertebrae; (2) C/A or C/P was less than 0.8; or (3) A/P was less than 0.75. Assessment of vertebral fractures was performed for T4 to L4.

Measurement of metacarpal BMD

An anteroposterior view radiograph of bilateral hands was taken of each subject using an aluminum step wedge (20 steps, 1 mm per step) as a standard. The BMD of the middle portion of the second metacarpus of the nondominant hand was measured with a computed X-ray densitometer (Teijin, Tokyo, Japan). The densitometer calculated BMD based on the graduations

on the aluminum step wedge, and BMD was expressed as the thickness of the aluminum equivalent (mm Al) with the same X-ray absorption. In this measurement, the coefficients of variation (100 × standard deviation/mean) for (1) intraobserver error, based on 10 consecutive measurements by 5 people, (2) daily change error, based on measurements performed on 10 consecutive days, and (3) X-ray picturing error, based on 10 exposures, were all within 1.3–3.8%.

Statistical analysis

Data are expressed as mean ± standard deviation. The significance of longitudinal changes in metacarpal BMD, and serum calcium, phosphorus, and ALP and urinary NTX levels was determined by one-way analysis of variance with repeated measurements. Comparisons of the characteristics and percent changes in urinary NTX level at 3 months between subjects who continued and discontinued alendronate treatment were performed using an unpaired *t* test. Factors contributing to the discontinuation of alendronate treatment were identified by logistic regression analysis. The independent variables were age, height, body weight, body mass index, years since menopause, BMD, % of young adult mean of BMD, serum calcium, phosphorus, and ALP levels, urinary NTX level, and the number of prevalent vertebral fractures. The dependent variables were continuation (input 0) and discontinuation (input 1) of alendronate treatment. Odds ratios and 95% confidence intervals were calculated. All statistical analyses were performed using the Excel Analysis 2008 Software (Social Survey Research Information Co., Ltd., Tokyo, Japan). A significance level of $p < 0.05$ was used for all comparisons.

Results

Discontinuation of alendronate treatment

During the 3-year period, 14 patients (19.4%) dropped out of the trial; 3 patients dropped out within 3 months, and 11 within 6 months. The reasons for dropping out were: side effects (diarrhea [$n=1$], gastric symptoms [$n=9$], and inflammation of the mouth [$n=1$]); or non-compliance ($n=3$). Logistic regression analysis showed that the number of prevalent vertebral fractures was a significant factor (odds ratio, 1.57; 95% confidence interval, 1.08–2.30; $p=0.020$) contributing to the discontinuation of alendronate treatment due to the reasons listed above (Table 2).

Table 3 shows the characteristics of both patients who continued and discontinued alendronate treatment. Only the number of vertebral fractures was greater in patients who continued alendronate treatment than in those who discontinued the treatment (2.0 ± 2.2 *vs.* 3.6 ± 2.2, respectively).

Table 2. Factors affecting discontinuation of alendronate treatment*

	OR	95% CI	*p*
Age (yr)	1.35	0.99–1.85	0.060
Height (m)	0.82	0.21–3.27	0.779
Body weight (kg)	1.51	0.18–12.56	0.704
Body mass index (kg/m^2)	0.41	0.00–42.24	0.705
Years since menopause	0.80	0.59–1.10	0.168
BMD (mm Al)	> 0.99	< 0.01– > 0.99	0.206
%YAM of BMD (%)	0.17	0.01–2.60	0.200
Serum calcium (mg/dL)	10.64	0.26–428.20	0.210
Serum phosphorus (mg/dL)	2.18	0.52–9.07	0.285
Serum ALP (IU/L)	0.99	0.98–1.00	0.138
Urinary NTX (nmol BCE/mmol Cr)	0.98	0.95–1.01	0.273
Vertebral fractures (*n*)	1.57	1.08–2.30	0.020

**Logistic regression analysis was used to identify factors affecting the discontinuation of alendronate treatment. OR = odds ratio; CI = confidence interval; BMD = bone mineral density; mm Al = aluminum equivalent; YAM = young adult mean; ALP = alkaline phosphatase; NTX = cross-linked N-terminal telopeptides of type I collagen; nmol BCE/mmol Cr = bone collagen equivalent per mmol of creatinine.*

Changes in BMD, serum calcium, phosphorus and ALP, and urinary NTX levels

Table 4 shows the longitudinal changes in metacarpal BMD, serum calcium, phosphorus and ALP, and urinary NTX levels. In 58 patients who continued the treatment for 3 years, the mean percentage change in urinary NTX level at 3 months was −44.1% compared with the baseline ($p < 0.0001$ by one-way analysis of variance with repeated measurements); the mean percentage change in serum ALP level compared with the baseline was −11.6% at 1 year, −11.8% at 2 years, and −12.5% at 3 years ($p < 0.0001$ by one-way analysis of variance with repeated measurements). However, the mean percentage change in metacarpal BMD compared with the baseline was + 0.5% at 1 year, + 0.0% at 2 years, and + 0.9% at 3 years with no significant changes ($p = 0.777$ by one-way analysis of variance with repeated measurements). Although serum calcium level significantly decreased ($p = 0.005$ by one-way analysis of variance with repeated measurements), serum phosphorus level did not significantly change ($p = 0.058$ by one-way analysis of variance with repeated measurements).

Urinary NTX data at 3 months were available for 11 patients who discontinued alendronate treatment

Table 3. Comparison of characteristics between subjects who continued and discontinued alendronate treatment*

	Continued ($n=58$)	Discontinued ($n=14$)	p
Age (yr)	72.8±6.1	75.9±3.9	0.074
Height (m)	1.47±0.06	1.48±0.06	0.752
Body weight (kg)	47.4±6.8	47.9±8.2	0.846
Body mass index (kg/m^2)	21.8±2.3	21.8±2.8	0.988
Years since menopause	22.4±5.8	23.9±4.6	0.354
BMD (mm Al)	1.88±0.24	1.88±0.25	0.970
BMD % of YAM (%)	68.5±8.5	68.7±9.1	0.954
Serum calcium (mg/dL)	8.9±0.3	9.0±0.3	0.456
Serum phosphorus (mg/dL)	3.6±0.6	3.6±0.7	0.873
Serum ALP (IU/L)	243±93	198±93	0.110
Urinary NTX (nmol BCE/mmol Cr)	70.7±31.5	62.3±32.5	0.375
Vertebral fractures (n)	2.0±2.2	3.6±2.2	0.016

**Data are presented as mean±standard deviation. BMD=bone mineral density; mm Al=aluminum equivalent; YAM=young adult mean; ALP=alkaline phosphatase; NTX=cross-linked N-terminal telopeptides of type I collagen; nmol BCE/mmol Cr=bone collagen equivalent per mmol of creatinine.*

Table 4. Changes in BMD and biochemical markers*

	Baseline	Mo 3	Yr 1	Yr 2	Yr 3	One-way ANOVA
BMD (mm Al)	1.88±0.23		1.89±0.25	1.88±0.25	1.89±0.23	0.777
(% change from baseline)			(0.5±4.8)	(0.0±3.8)	(0.9±7.1)	
Serum calcium (mg/dL)	9.1±0.5		8.9±0.4	8.8±0.4	8.9±0.4	0.005
(% change from baseline)			(–1.8±5.2)	(–2.0±5.6)	(–1.1±6.0)	
Serum phosphorus (mg/dL)	3.6±0.6		3.7±0.7	3.4±0.5	3.5±0.5	0.058
(% change from baseline)			(5.7±22.0)	(–3.3±11.3)	(0.0±19.7)	
Serum ALP (IU/L)	243±93		208±66	206±65	201±57	<0.0001
(% change from baseline)			(–11.6±16.4)	(–11.8±17.1)	(–12.5±19.1)	
Urinary NTX (nmol BCE/mmol Cr)	70.7±31.5	36.7±16.1				<0.0001
(% change from baseline)		(–44.1±23.6)				

**Data are presented as mean ± standard deviation and one-way ANOVA with repeated measurements was used to determine the significance of longitudinal changes in BMD and biochemical markers. BMD = bone mineral density; mm Al = aluminum equivalent; ALP = alkaline phosphatase; NTX = cross-linked N-terminal telopeptides of type I collagen; nmol BCE/mmol Cr = bone collagen equivalent per mmol of creatinine.*

within 6 months. The mean percent change in urinary NTX level at 3 months compared with the baseline in those patients was −40.2% ($p<0.0001$ by one-way analysis of variance with repeated measurements). However, the unpaired t test showed that there was no significant difference in changes to this parameter between patients who continued and discontinued alendronate treatment ($p=0.614$).

Discussion

This cohort study showed that alendronate treatment decreased urinary NTX and serum ALP levels, and maintained metacarpal BMD in postmenopausal Japanese women with osteoporosis. The majority of patients adhered well to alendronate treatment in our clinic. The number of prevalent vertebral fractures was a significant factor affecting the discontinuation of alendronate treatment due to side effects and non-compliance.

Choices in osteoporosis treatment usually derive from evidence-based medicine and the results of systematic reviews and meta-analyses are considered critical evidence when determining treatment type. Such meta-analysis studies have shown that alendronate is an efficacious agent for reducing the risk of vertebral, nonvertebral, and hip fractures in postmenopausal osteoporotic women. The risk reduction rate is 48%, 49%, and 55%, respectively.[9–11] For this reason, we chose alendronate for our patients. Had parathyroid hormone been available in Japan at the time our study was carried out, we might have considered this option, but it was not.

The response of BMD to alendronate appears to differ among skeletal sites. Tucci et al[12] have reported that the effect of alendronate on BMD in postmenopausal women with osteoporosis is greater in the lumbar

spine than in the femoral neck, and seems to be least in the forearm. The mean improvement in BMD from baseline after 3 years of treatment with alendronate (10 mg daily) was 9.59% in the lumbar spine, 4.66% in the femoral neck, 7.38% in the femoral trochanter, 4.97% in the total hip, and 0.32% in the forearm (distal third of the forearm). In our study, the mean improvement in metacarpal and lumbar BMD after 3 years of treatment with alendronate was 0.9%. This change was smaller than those observed in other skeletal sites.

Because the normal range of urinary NTX level in Japanese women is 9.3–54.3 nmol of bone collagen equivalent per mmol of creatinine,[13] our patients were considered to show high bone turnover osteoporosis (mean urinary NTX level: 70.7 nmol of bone collagen equivalent per mmol of creatinine). Alendronate treatment successfully reduced urinary NTX levels by 44.1% at 3 months, a greater reduction than the minimum significant change (35%). Serum ALP was less sensitive to alendronate treatment than urinary NTX. However, alendronate treatment failed to increase metacarpal BMD in postmenopausal women with osteoporosis. The minimal effect of alendronate treatment on BMD in the metacarpus might be associated with the following factors: the type of bone (appendicular or axial bone), the ratio of cancellous to cortical bone, and the low reproducibility of BMD measurements.[14] If the lumbar spine had been evaluated as a BMD measurement site, patients might have experienced an increase in BMD.[14]

Adherence of our patients to alendronate treatment was better than previously reported.[15,16] One reason for this may be that most of the patients came to our outpatient clinic once or twice a week to undergo physical therapies for symptoms related to osteoporosis, spondylosis, and osteoarthritis, and were encouraged by the GP to continue treatment. Another reason may have been that our informed consent documentation also encouraged patients to continue treatment by stating the following: (1) treatment with bisphosphonates such as alendronate is recommended because high bone turnover in postmenopausal women with osteoporosis can increase the incidence of vertebral fractures, resulting in disability and mortality; (2) long-term treatment with alendronate may be effective in preventing osteoporotic fractures including vertebral and hip fractures that might occur in later life (this is supported by a recent report);[17] (3) reducing bone turnover (as especially indicated by a reduction in urinary NTX levels) could be more important than increasing BMD to prevent vertebral fractures;[18–20] (4) patients should take the medicine according to our instructions to avoid serious side effects and to achieve a satisfactory outcome. In addition, the method for taking the medicine was explained (with the aid of a pamphlet) by both a doctor and a pharmacist. Thus, education and communication are important to improve patient compliance. However, the satisfactory results of repeated measurements of urinary NTX level might not contribute to continuation of alendronate treatment, because there was no statistically significant difference to changes in urinary NTX level between patients who continued and those who discontinued alendronate treatment.

Previously, the main factors contributing to the discontinuation of alendronate treatment in postmenopausal women with osteoporosis were adverse gastrointestinal events and age.[15,16,21] The factors contributing to discontinuation in our study were: side effects (diarrhea [$n=1$], gastric symptoms [$n=9$], and inflammation of the mouth [$n=1$]) or non-compliance ($n=3$), with gastrointestinal adverse events being the most significant. The results of logistic regression analysis showed that the number of prevalent vertebral fractures was a significant factor that influenced the discontinuation of alendronate treatment. Contrary to our expectations, the mean number of prevalent vertebral fractures was greater in patients who continued alendronate treatment than those who discontinued the treatment. However, the threshold number for vertebral fractures remains uncertain. Finally, a family history of osteoporotic fractures could influence the level of treatment adherence, although this factor was not included in the analysis.

Recently, a higher incidence of esophageal hiatal hernia and gastroesophageal reflux disease has been reported in postmenopausal women. The presence and severity of vertebral fractures are also associated with the presence of esophageal hiatal hernia in postmenopausal women,[22] and the prevalence of gastroesophageal reflux is increased in elderly women.[23] We surmise that because women with multiple vertebral fractures might often have gastroesophageal problems, this may contribute to difficulty in taking medicine and low adherence. It could be that elderly, osteoporotic women had been suffering from severe osteoporosis for a long time, and that the number of these patients' prevalent vertebral fractures was a significant factor in their decision to discontinue alendronate treatment.

Intravenous bisphosphonates such as zoledronate and ibandronate may be useful in preventing adverse gastrointestinal events and to improve compliance because of their convenient dosing regimens. Therefore, these agents could be first line drugs in patients who have a risk of adverse gastrointestinal events or non-compliance with oral bisphosphonates treatment.

The limitations of this research include the fact that this trial was carried out by a GP at a local outpatient clinic so the study was not a placebo-controlled trial but a cohort study. Second, the sample size was determined by the number of subjects available rather than on the basis of the sample size required for statistical validity, and may have been too small to draw valid conclusions. Therefore, our results should not be extrapolated to the population at large. However, we believe that the significant results from our research should be made available to Japanese GPs working in local outpatient clinics because the patient characteristics and methods of monitoring and follow-up may be similar to ours. Further studies are needed to confirm our results.

In conclusion, this study showed that alendronate treatment decreased urinary NTX and serum ALP levels, and maintained metacarpal BMD in postmenopausal Japanese women with osteoporosis. The patients adhered well to alendronate treatment in our clinic. The number of prevalent vertebral fractures was an important factor affecting the discontinuation of alendronate treatment due to side effects and non-compliance.

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