Longterm Effect of Intermittent Cyclical Etidronate Therapy on Corticosteroid-Induced Osteoporosis in Japanese Patients with Connective Tissue Disease: 7-Year Followup

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ABSTRACT. ***Objective.*** To determine the efficacy and safety of intermittent cyclical etidronate therapy of up to 7 years for corticosteroid-induced osteoporosis.

Methods. One hundred two Japanese patients who originally participated in a 3-year prospective randomized study were enrolled into an open-label followup study. All patients had received > 7.5 mg of prednisolone daily for at least 90 days before entry into the original study and were randomly assigned to 2 treatment arms: E, those receiving etidronate disodium (200 mg per day) for 2 weeks together with 3.0 g of calcium lactate and 0.75 μg of alphacalcidol daily; and C, controls receiving only the latter. Endpoints included changes from baseline in bone mineral density (BMD) of the lumbar spine and the rate of new vertebral fractures.

Results. The mean (± SD) lumbar spine BMD had increased by 5.9% ± 8.8% (p = 0.00007) and 2.2% ± 5.8% (p = 0.013) from baseline after 7 years in groups E and C, respectively. This improvement in BMD in group E was significantly better than in group C (p = 0.02). The frequency of new vertebral fractures was lower in group E, resulting in reduction of the risk of such new fractures by 67% at year 7 (odds ratio 3.000; 95% confidence interval, 0.604–14.90; p = 0.18). There were no severe adverse events in group E during our study.

Conclusion. Our results indicate that longterm (up to 7 years) intermittent cyclical etidronate therapy is safe and effective for prevention and treatment of corticosteroid-induced osteoporosis in patients with connective tissue diseases. (First Release Nov 15 2007; J Rheumatol 2008;35:142–6)

Key Indexing Terms:
CORTICOSTEROID-INDUCED OSTEOPOROSIS
BISPHOSPHONATE
BONE MINERAL DENSITY
CONNECTIVE TISSUE DISEASES

Longterm corticosteroid treatment in patients with connective tissue disease (CTD) causes osteoporosis as the major adverse event. Bisphosphonate therapy has proven to be effective in both prevention and treatment of corticosteroid-induced osteoporosis (CIOP)[1-4]. Guidelines for treating patients with CIOP recommend the use of bisphosphonates as a first-line drug[5]. Nitrogen-containing bisphosphonates, such as alendronate or risedronate, have proven efficacy for both prevention and treatment of CIOP. However, use of these bisphosphonates is associated with gastrointestinal adverse events[6]. We previously conducted a 3-year prospective randomized study to determine the efficacy and safety of etidronate (the first available nitrogen-free bisphosphonate) for treating CIOP[7]. Although longterm followup (7 yrs) of intermittent cyclical etidronate therapy in patients with postmenopausal osteoporosis has been reported[8], few studies are available on the longterm effects of etidronate in patients with CIOP[9]. Further, there are no reports on the continued effectiveness and safety of etidronate for CIOP in patients with CTD. For this reason, we have followed up the original 3-year prospective study for an additional 4 years to determine the longterm efficacy of intermittent cyclical etidronate for treating CIOP in patients with CTD.

MATERIALS AND METHODS

Patients. In the original 3-year study, 102 patients with different CTD were enrolled (56 with systemic lupus erythematosus; 12 rheumatoid arthritis; 10 polymyositis/dermatomyositis; 9 vasculitis syndrome; 8 adult-onset Still disease; 5 polymyalgia rheumatica; 1 systemic sclerosis; and 1 Sjögren's syndrome). Patients' ages ranged from 21 to 73 years and they had been taking

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Accepted for publication September 7, 2007.

> 7.5 mg of prednisolone (PSL) daily for at least 90 days. The results of this study have been reported elsewhere[7].

Study design. In the original 3-year prospective randomized study, all patients were randomly assigned to one of 2 investigational groups. Patients in the etidronate group (E) received 200 mg/day etidronate disodium (Didronel, Sumitomo Pharmaceuticals, Osaka, Japan) for 2 weeks, together with 3.0 g of calcium lactate and 0.75 μg of alphacalcidol (Alfarol, Chugai Pharmaceuticals, Tokyo, Japan) daily for 90 days. This cycle was repeated 28 times during the 7-year observation period. Patients were instructed to take their medication with water at bedtime. The control group (C) received only 3.0 g of calcium lactate and 0.75 μg of alphacalcidol daily for 90 days. In the followup study, the patients were to continue taking the same treatments to which they had been assigned earlier. However, a change of treatment was allowed if their doctor decided that it was necessary for treatment. All patients had provided written informed consent.

Bone mineral density (BMD) and radiological measurements. Lateral and anteroposterior lumbar and thoracic spine radiographs were taken and evaluated at Keio University Hospital at baseline and every year for 7 years. All lumbar and thoracic spine images were evaluated by experienced physicians who were blinded to treatment assignments. The diagnosis of vertebral fracture and osteoporosis was based on the criteria defined by the Japanese Society for Bone and Mineral Research in 1996[10]. A vertebral fracture was defined as: (1) The ratio of the central height (C) to the anterior height (A) of the vertebra was less than 0.8, or the ratio of C to the posterior height (P) was less than 0.8. (2) The ratio of A to P was less than 0.75. (3) A crushed vertebra was recorded when its height was reduced by more than 20% in either A, C, or P compared with the adjacent vertebrae.

Classification of BMD was based on the following criteria: Normal BMD: > 80% of the young adult mean (YAM). Osteopenia: between 70% and 80% of YAM. Osteoporosis: < 70% of YAM.

This definition of osteoporosis (i.e., < 70% of YAM) also corresponds to the osteoporosis criteria recommended by the World Health Organization [less than –2.5 standard deviation (SD) of YAM]. All BMD measurements were made by dual-energy x-ray absorptiometry using an XR-36 (Norland Medical Systems, Fort Atkinson, WI, USA). Because we had already documented changes in bone formation and bone absorption markers in the original 3-year prospective randomized study, we did not monitor biochemical markers of bone turnover in this followup study.

Statistical analysis. The baseline characteristics and homogeneity of the patients' background in an intent-to-treat population was compared between the 2 investigational groups by chi-square test, Student's t-test, and Mann-Whitney U-test, as appropriate. Regardless of whether patients were still receiving the assigned medication, all available BMD data were used to perform an intent-to-treat analysis. If the measurement of the lumbar spine BMD at 7 years was not available, the measurement obtained at the time closest to this was used in the analysis. The patients whose BMD data could not be evaluated correctly because of previous compression fractures are excluded from the analysis. The primary efficacy analysis was based on the differences between the 2 investigational groups in the percentage change of lumbar spine BMD (L2-L4) from baseline to last measurement. The percentage change of BMD from the baseline was compared by an analysis of variance model (SPSS version 14.0). The comparison of percentage change of BMD between the 2 groups was calculated by Student's t-test. Odds ratios adjusted by menopausal status stratum as a factor were calculated for differences of the incidence of vertebral fractures at 7 years between the 2 treatment groups. Significance level was set at 5% and all results expressed as mean ± SD.

RESULTS

At the beginning of this followup study, 7 patients in group E and 6 patients in group C could not be included because of death or loss to followup. There were no significant differences between groups in baseline characteristics in that subset of patients whose data could be used for an intent-to-treat analysis (43 and 45 in groups E and C whose BMD data were available, respectively; Table 1). During 7 years, the average daily dose of PSL in each year was not significantly different between the 2 groups. The number of patients taking steroid in groups E and C was also not significantly different (Table 2). During the followup study, there were no adverse events in either group. However, 2 patients in group E and one in group C died due to progression of their underlying CTD or infection during this study. Ten patients in group C began to receive bisphosphonate as well as alphacalcidol and calcium lactate because their rheumatologist decided that they would benefit from such treatment. On the other hand, only 1 patient in group E was changed from etidronate to alendronate.

After 7 years of treatment, the mean (± SD) percentage change in BMD of the lumbar spine in group E (5.9% ± 8.8%) was significant compared to baseline ($p = 0.00007$). This was also the case, albeit to a lesser extent (2.2% ± 5.8%), in group C ($p = 0.013$; Figure 1). This improvement of BMD was significantly greater in group E than in group C ($p = 0.02$).

In a separate analysis of premenopausal and postmenopausal women, both of these subgroups of group E showed an increase in the mean percentage change in BMD during their treatment course. In premenopausal women, both groups E and C had significant increases of lumbar spine BMD from baseline at 7 years ($p = 0.001$ and $p = 0.02$, respectively). These increases were significantly higher in group E than C in a subgroup of premenopausal women (6.7% ± 9.1% vs 2.3% ± 4.5%; $p = 0.04$). Although the postmenopausal subgroup of group E showed an increase in BMD of the lumbar spine, this failed to achieve significance (2.8% ± 8.0%; $p = 0.23$). BMD of this subgroup in group C remained at baseline (–0.03% ± 7.60%; $p = 0.99$). There were also no significant differences between the 2 groups in this respect.

Analysis of the subgroups based on the baseline BMD revealed that the osteoporosis + osteopenia subgroup in group E showed a significant increase of the lumbar spine BMD from baseline at 7 years ($p = 0.0009$). This increase was significantly greater in group E than in group C at 7 years (7.8% ± 9.5% vs 2.0% ± 6.3%; $p = 0.04$). Both E and C groups of the normal BMD subgroup showed significant increases in lumbar spine BMD at year 7 (3.9% ± 7.7%, $p = 0.03$ and 2.4% ± 5.6%, $p = 0.03$, respectively). Again, there were no significant differences between the 2 groups ($p = 0.40$).

The mean percentage change in lumbar spine BMD in group E improved from baseline by approximately 5% over the 7 years (Figure 2). Although group C showed no decrease of BMD from baseline, the increase in group E was significantly greater than in group C at 7 years ($p = 0.02$).

Six patients in group C had a total of 11 new vertebral fractures during the followup period (Table 3), whereas only 2 patients in group E had a total of 3 new fractures. At year 7, cyclic etidronate therapy had reduced the risk of new vertebral fracture by 67% [odds ratio (OR) 3.00; 95% confidence inter-

Table 1. Baseline characteristics at the beginning of the followup study (values are means ± SD).

Characteristics	Group E, n = 46	Group C, n = 45	p
Men, n(%)	6 (13)	8 (18)	NS
Premenopausal women, n (%)	25 (54)	24 (53)	NS
Postmenopausal women, n (%)	15 (33)	13 (29)	NS
Mean age, yrs			
Men	53 ± 17	43 ± 16	NS
Women	43 ± 14	43 ± 13	NS
Total corticosteroid dose, mg			
Men	2,577 ± 1245	1,705 ± 497	NS
Premenopausal women	2,497 ± 1816	1,852 + 506	NS
Postmenopausal women	2,143 ± 918	1,880 ± 931	NS
Lumbar spine BMD, g/cm^2			
Men	0.95 ± 0.17	0.90 ± 0.18	NS
Premenopausal women	0.86 ± 0.18	0.93 ± 0.14	NS
Postmenopausal women	0.78 ± 0.15	0.79 ± 0.14	NS

Group E: etidronate; Group C: control. BMD: bone mineral density; NS: not significant; SD: standard deviation.

Table 2. Average daily dose of PSL and ratio of patients still receiving corticosteroids (years after start of the prospective study).

Year		1	2	3	4	5	6	7
Average daily dose of PSL (mg/day, mean ± SD)	Group E	10.7 ± 3.8	9.4 ± 5.4	8.3 ± 3.8	7.7 ± 3.1	8.1 ± 4.0	9.3 ± 5.1	8.5 ± 4.4
	Group C	9.7 ± 3.7	8.1 ± 2.8	8.0 ± 3.3	7.8 ± 4.1	7.7 ± 4.1	8.0 ± 4.6	7.7 ± 3.4
	p value	NS	NS	NS	NS	NS	NS	NS
Ratio of patients receiving PSL (%)	Group E	100	100	100	98	95	92	92
	Group C	100	100	100	98	98	98	95
	p value	NS	NS	NS	NS	NS	NS	NS

Group E: etidronate; Group C: control. PSL: prednisolone; NS: not significant.

val 0.604–14.90; p = 0.18). The adjusted OR by menopausal status was calculated as 2.05.

There were no adverse events in group C, but 2 occurred in group E during the 3-year prospective study. However, there were no adverse events in either group during the followup period. Although serum calcium monitoring had not been performed systematically, where measured, no hypercalcemia was found in either group. None of the patients had gastrointestinal symptoms severe enough to discontinue the etidronate throughout the entire 7 years of followup in group E.

DISCUSSION

Our study demonstrated that longterm intermittent cyclical etidronate therapy increased the BMD of the lumbar spine in Japanese patients with CIOP. No significant reduction in risk of vertebral fractures at 7 years was achieved. However, this might be due to small sample size; future studies on larger numbers of patients will be required to draw a definitive conclusion on this point.

It has been reported before that etidronate increases BMD in CIOP[11-15], but there is only one report on longterm observation indicating efficacy of continuing etidronate therapy for more than 5 years in patients with asthma receiving oral and/or inhaled corticosteroids[9]. The longterm efficacy of intermittent etidronate therapy for CIOP in patients with CTD has to our knowledge never been evaluated. Ours is thus the first comprehensive study on the efficacy of longterm cyclical etidronate therapy of up to 7 years for CIOP in patients with CTD. Previous studies showed that alendronate or risedronate, which are both nitrogen-containing bisphosphonates, can maintain continuing increases in BMD, as well as effect a reduction of the fracture rate[4,16-19]. Our study is consistent with these findings with respect to maintaining BMD.

In our study, both groups C and E showed higher increases in lumbar spine BMD at years 6 and 7. In group C, it might be due to the fact that 9 patients added bisphosphonates besides activated vitamin D_3 during the followup study. Indeed, the mean percentage changes in patients who added bisphosphonates were higher compared with those patients who did not at year 7, although the differences were not statistically significant. In contrast, only 1 patient changed from etidronate to alendronate in group E. However, this patient and 2 patients who discontinued the corticosteroids during the followup study showed considerable increases in lumbar

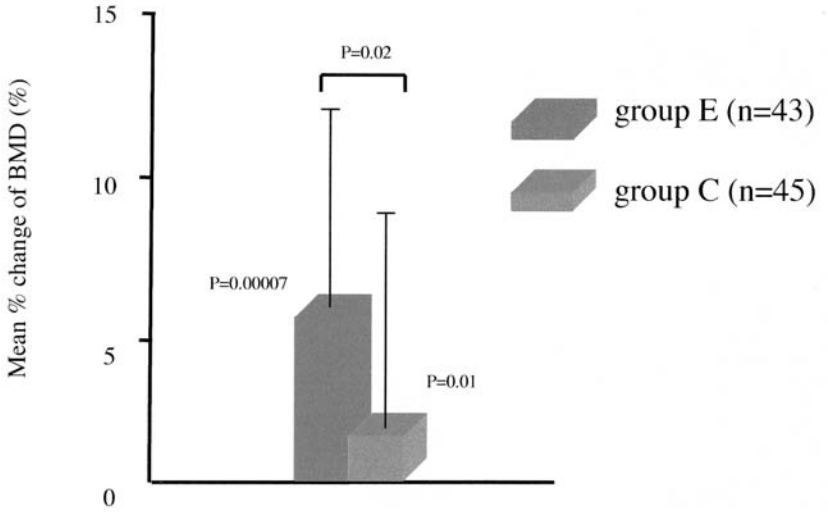

Figure 1. The mean (± SD) percentage change in bone mineral density (BMD) of the lumbar spine between baseline (0 yr) and 7 years of groups E and C. In all patients, the mean (± SD) percentage change in BMD of the lumbar spine increased 5.9% ± 8.8% (p = 0.00007) from baseline at 7 years in group E and 2.2% ± 5.8% (p = 0.013) in group C. The improvement of BMD in group E was significantly higher than in group C at 7 years (p = 0.02).

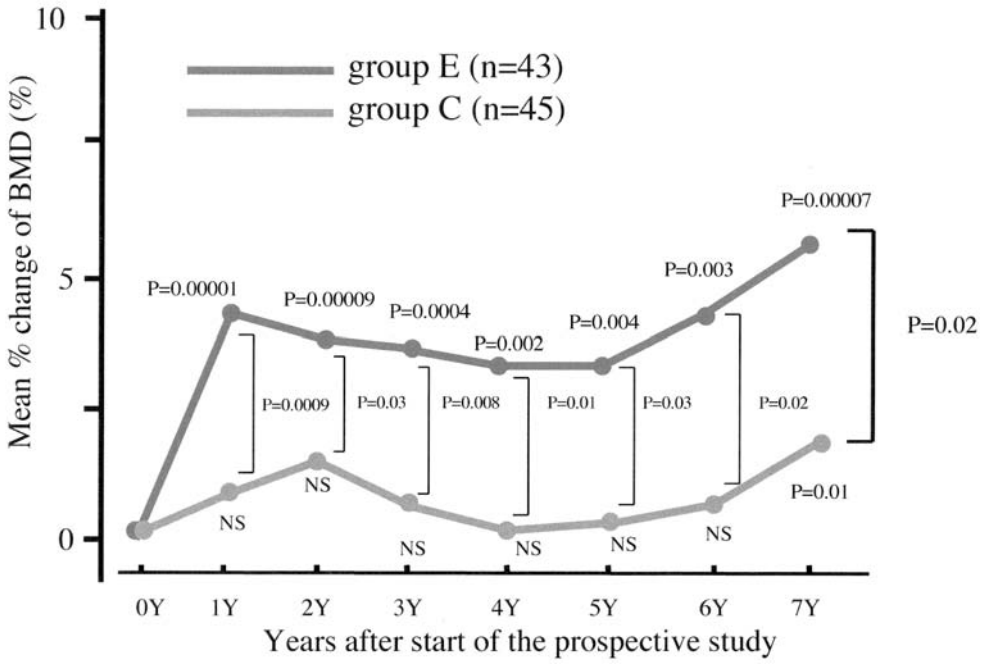

Figure 2. The mean percentage change in lumbar spine BMD in group E improved from baseline by approximately 5% over the 7-year study.

spine BMD at years 6 or 7. These increases in lumbar spine BMD might have contributed to the increase in the mean percentage change of lumbar spine BMD to some degree. As far as we know, there were no patients who took other medications. Persistent prescriptions for etidronate and activated vitamin D_3 have been confirmed in the medical records. Therefore, we think that other medications or compliance with treatment would not affect the BMD data in either group.

The ability of activated vitamin D_3 to prevent the loss of BMD caused by corticosteroids has been reported[20]. In our study, the control group (receiving activated vitamin D_3) slightly increased their lumbar spine BMD and maintained this for 7 years. However, as there was no placebo control in our study, we could not compare the rate of vertebral fracture in the group receiving activated vitamin D_3 to that of the placebo group.

Table 3. Incidence of vertebral fractures at 7 years in group E (etidronate) and C (control).

	Group E	Group C
Male	0/4	1/6
Female		
Premenopausal	1/24	1/23
Postmenopausal	1/10	4/13
Total	2/38	6/42
Total vertebral fracture	3	11

A randomized, double-blinded, multicenter study showed almost the same efficacy of either 200 mg or 400 mg of cyclical intermittent etidronate therapy in Japanese patients with involutional osteoporosis[21]. The current approved dose of etidronate for osteoporosis in Japan is 200 mg daily. When the dose of 200 mg of etidronate was ineffective or the patients had severe osteoporosis, 400 mg was used. Our results here indicated that 200 mg of etidronate was sufficiently effective to prevent or treat Japanese patients with CIOP. This might be due to racial differences or the difference in the dose per unit body weight between Japanese and Caucasian patients. Because our study did not include large numbers of patients, further observations will be needed to confirm this hypothesis.

Regarding adverse events, it was notable that severe side effects were not seen throughout the 7 years of the study. No gastrointestinal disorders, bone necrosis, or disturbance of bone formation was recorded. Only 2 patients had an adverse event of any kind in group E during the 3-year prospective study. No other patients dropped out of the study because of drug intolerance or discomfort. Treatment compliance was good and we can conclude that intermittent cyclical etidronate therapy is very well tolerated. Moreover, in view of its cost-effectiveness[22], cyclical intermittent etidronate therapy should be considered as a routine treatment option for CIOP, especially in patients with previous or current gastrointestinal disorders.

Intermittent cyclical etidronate therapy significantly increased BMD of the lumbar spine and maintained it over 7 years in patients with CIOP. There was a tendency towards a reduction in the incidence of vertebral fractures at 7 years in etidronate-treated patients compared to activated vitamin D_3-treated patients, but this did not achieve statistical significance. Longterm intermittent cyclical etidronate therapy is a safe, well tolerated, and effective therapy for the prevention and treatment of CIOP in Japanese patients with CTD.

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