Effect of Intermittent Cyclical Etidronate Therapy on Corticosteroid Induced Osteoporosis in Japanese Patients with Connective Tissue Disease: 3 Year Followup

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ABSTRACT. ***Objective.*** A 3 year prospective randomized study was conducted to clarify the efficacy of intermittent cyclical etidronate therapy on corticosteroid induced osteoporosis.

Methods. A group of 102 Japanese patients were enrolled, each taking > 7.5 mg of prednisolone daily for at least 90 days. Patients were randomly divided into 2 treatment groups: Group E (etidronate) took 200 mg etidronate disodium per day for 2 weeks with 3.0 g calcium lactate and 0.75 µg alphacalcidol daily; Group C (control) took 3.0 g calcium lactate and 0.75 µg alphacalcidol daily. Outcome measurements included changes from baseline in bone mineral density (BMD) of the lumbar spine and the rate of new vertebral fractures at 48 and 144 weeks.

Results. The mean (± SD) lumbar spine BMD increased 3.7 ± 5.6% ($p < 0.01$) and 1.5 ± 4.1% (NS) from baseline at 48 weeks and 4.8 ± 6.9% ($p < 0.005$) and 0.4 ± 5.0% (NS) from baseline at 144 weeks in Group E and Group C, respectively. The improvement of BMD in Group E was significantly greater than in Group C at 144 weeks ($p < 0.01$). In 3 subgroups, men and premenopausal and postmenopausal women, the postmenopausal women showed the greatest improvement. Mean percentage change in this subgroup was 10.1 ± 8.0% and 1.35 ± 6.4% in Group E and Group C, respectively. We noted that 2 patients in Group C had new vertebral fractures, whereas no fractures were observed in Group E.

Conclusion. These results indicate that intermittent cyclical etidronate therapy is effective for the prevention and treatment of corticosteroid induced osteoporosis in patients with connective tissue diseases. (J Rheumatol 2003;30:2673–9)

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

Osteoporosis is one of the major adverse effects caused by longterm corticosteroid treatment for connective tissue disease. Recently the efficacy of bisphosphonate, activated vitamin D_3, calcitonin, and hormone replacement therapy on corticosteroid induced osteoporosis has been reported[1-15]. Among these agents, bisphosphonate therapy has been reported as beneficial in both the prevention and treatment of corticosteroid induced osteoporosis[3,5,13,14]. Although several studies have reported the effect of etidronate for corticosteroid induced osteoporosis in North America[1-4,7,10], a longterm (> 3 years) observation has never been reported. Further, few studies are available on the effect of etidronate in Japanese patients with corticosteroid induced osteoporosis, and the differences between Japanese and Caucasian populations in the efficacy of etidronate are unknown. In one study, the effects of alendronate, one of the bisphosphonates, in Japanese patients were similar to those seen in Caucasian patients[16]. For this reason, we conducted a 3-year prospective randomized study to determine the prevention and treatment efficacy of intermittent cyclical etidronate therapy on corticosteroid induced osteoporosis.

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MATERIALS AND METHODS

Patients. Patients were 21 to 73 years of age, had underlying connective tissue diseases (systemic lupus erythematosus, n = 56, rheumatoid arthritis 12, polymyositis/dermatomyositis 10, vasculitis syndrome 9, adult onset Still's disease 8, polymyalgia rheumatica 5, systemic sclerosis 1, Sjögren's syndrome 1), and had taken > 7.5 mg prednisolone daily for at least 90 days. Patients were excluded if they had abnormalities on spinal radiographs that prevented accurate measurements of the lumbar spine bone mineral density (BMD) by dual-energy x-ray absorptiometry (DEXA), had

severe cardiac disease or renal insufficiency, or had taken medications known to affect bone metabolism within the preceding year. Written informed consent was obtained from all patients.

Study design. In this 3-year prospective randomized study, the patients were classified according to sex and menopausal status (i.e., men, premenopausal women, postmenopausal women). All patients were randomly assigned to one of 2 investigational groups: Group E (etidronate), who took etidronate disodium (200 mg/day; Didronel, Sumitomo Pharmaceuticals, Osaka, Japan) for 2 weeks with 3.0 g calcium lactate and 0.75 µg alphacalcidol (Alfarol, Chugai Pharmaceuticals, Tokyo, Japan) daily for 90 days; or Group C (control), who took 3.0 g calcium lactate and 0.75 µg alphacalcidol daily for 90 days. This cycle was repeated 12 times during the 3-year treatment period. Patients were instructed to take the study drug with water at bedtime.

BMD and radiological measurements. Radiographs of the lateral and anteroposterior lumbar and thoracic spine were taken and evaluated at Keio University Hospital at baseline and at 48 weeks and 144 weeks. All radiographs were evaluated by experienced skeletal physicians who were blinded to treatment assignments. The diagnosis of vertebral fracture and osteoporosis was based on diagnostic criteria defined by the Japanese Society for Bone and Mineral Research in 1996[17].

A vertebral fracture was defined as follows: (1) The ratio of the central height of the vertebra (C) and the anterior height of the vertebra (A) was less than 0.8 or the ratio of C and the posterior height of the vertebra (P) was less than 0.8. (2) The ratio of A and P was less than 0.75. (3) Crush vertebra was defined when the height of the vertebrae was reduced more than 20% in either A, C, or P compared with the adjacent vertebrae.

The classification of BMD was based on the following criteria: (1) Normal BMD: > 80% of the young adult mean (YAM). (2) Osteopenia: between 70% and 80% of YAM. (3) Osteoporosis: < 70% of YAM.

Based on these criteria, the definition of osteoporosis (i.e., < 70% of YAM) corresponds to the osteoporosis criteria recommended by the World Health Organization (i.e., < –2.5 SD of YAM).

All measurements of BMD were made by DEXA using the XR-36 (Norland Medical Systems, Fort Atkinson, WI, USA). The primary outcome was the difference between the 2 investigational groups at Weeks 48 and 144 as compared with baseline in the mean percentage change of the lumbar spine BMD (L2–L4).

Markers of bone turnover. Serum and urine samples were obtained at baseline and at 24 weeks for measurement of biochemical markers of bone turnover. Alkaline phosphatase (ALP) isozymes were separated on a cellulose-acetate membrane with Tris-barbital buffer. Enzyme staining was carried out on 5-bromo-3-indoxylphosphate p-toluidine salts. Quantitation of bone ALP (BAP) isozyme was performed using a transmission densitometer (EDC; Helena Laboratories, Saitama, Japan) connected to a microcomputer and urinary excretion of deoxypyridinoline (Dpd) (Pyrilinks-D, Quidel Corp., San Diego, CA, USA). All analysis was done at Keio University.

Statistical analysis. An intent-to-treat analysis was performed. The baseline characteristics and homogeneity of the patients' background were compared between the 2 investigational groups by Student t test and Wilcoxon rank-sum test. The main efficacy analysis was the percentage change of BMD from baseline to last measurement. If the measurement of the lumbar spine BMD at Week 144 was not available, the measurement obtained at Week 48 was used in the analysis. The percentage change of BMD of each group was determined by paired t test and comparison of percentage change of BMD between the 2 groups was calculated by Student t test. Significance level was set at 5% and all results were expressed as mean ± standard deviation.

RESULTS

A set of 51 patients were randomly assigned to each group to receive either etidronate + calcium lactate + alphacalcidol (Group E) or calcium lactate + alphacalcidol (Group C). There were no significant differences in baseline characteristics in either investigational group (Table 1). The cumulative corticosteroid dose in Group E 6 months before the study was 2199 ± 855 mg, and in Group C 1784 ± 655 mg. The number of patients with compression fractures at baseline was 5 (13%) in Group E and 4 (10%) in Group C. This finding was not statistically significant. Twenty-two patients in Group E and 24 patients in Group C withdrew before study completion. Among these patients, 13 patients in Group E and 14 in Group C were dropped from the study due to protocol violations. Two patients in Group E withdrew because of adverse events; one experienced a headache and the other developed a facial rash. Two patients in each group died during the study. These deaths were attributed to progression of their underlying connective tissue disease. The baseline characteristics of those that dropped out were not significantly different from those that continued.

At baseline, lumbar spine BMD in the women ranged from 0.534 to 1.333 g/cm^2 (mean 0.846 ± 0.166 g/cm^2). Among 88 women, 71 (81%) were below the average of age matched normal individuals. Twenty-two (25%) were diagnosed as having osteopenia; 23 (26%) were diagnosed as osteoporosis.

In Group E, the mean (± SD) percentage change in BMD of the lumbar spine significantly increased 3.7 ± 5.6% ($p < 0.01$) and 4.8 ± 6.9% ($p < 0.005$) from baseline at 48 weeks and 144 weeks, respectively (Figure 1). The improvement of BMD in Group E was significantly higher than in Group C at 144 weeks ($p < 0.01$). In Group E, the mean percentage change of the lumbar spine BMD at 144 weeks was greater than at 48 weeks, whereas in Group C there was a decrease at 144 weeks compared to 48 weeks.

When classified into 3 subgroups (men, premenopausal women, postmenopausal women) (Figure 2), all subgroups of Group E showed an increase in the mean percentage change in BMD during their course. Among these subgroups, the postmenopausal women of Group E showed the greatest improvement. In the subgroups of premenopausal women and postmenopausal women, the increase of mean percentage change was significantly greater in Group E than in Group C at 144 weeks: 3.8 ± 6.6% vs –0.2 ± 4.8% ($p < 0.01$) and 10.1 ± 8.0% vs 1.4 ± 6.4% ($p < 0.05$), respectively.

Analysis of the subgroups of women based on the baseline BMD (osteoporosis + osteopenia, and normal BMD) revealed that Group E women with osteoporosis + osteopenia showed a significant increase of the lumbar spine BMD from baseline. The greatest improvement was seen at 144 weeks. In both subgroups of osteoporosis + osteopenia and normal BMD, the increase of mean (± SD) percentage change was significantly greater in Group E than in Group C at 144 weeks: 5.8 ± 7.2% vs 0.9 ± 5.1% ($p < 0.05$) and 4.1 ± 7.2% vs –1.7 ± 5.1% ($p < 0.05$), respectively.

Table 1. Baseline characteristics of patients in Group E and Group C. Values are means ± SD or percentages.

Characteristics	Group E, n = 51	Group C, n = 51	p
Men, n (%)	4 (10)	5 (13)	NS
Premenopausal women, n (%)	24 (60)	21 (52)	NS
Postmenopausal women, n (%)	12 (30)	14 (35)	NS
Age, yrs			
Men	49 ± 23	45 ± 17	NS
Women	42 ± 13	44 ± 12	NS
Total corticosteroid dose, mg	2,199 ± 855	1,784 ± 655	NS
Lumbar spine BMD, g/cm^2			
Men	0.92 ± 0.22	0.85 ± 0.14	NS
Premenopausal women	0.88 ± 0.19	0.90 ± 0.14	NS
Postmenopausal women	0.77 ± 0.12	0.75 ± 0.15	NS
Vertebral fractures, n (%)	5 (13)	4 (10)	NS

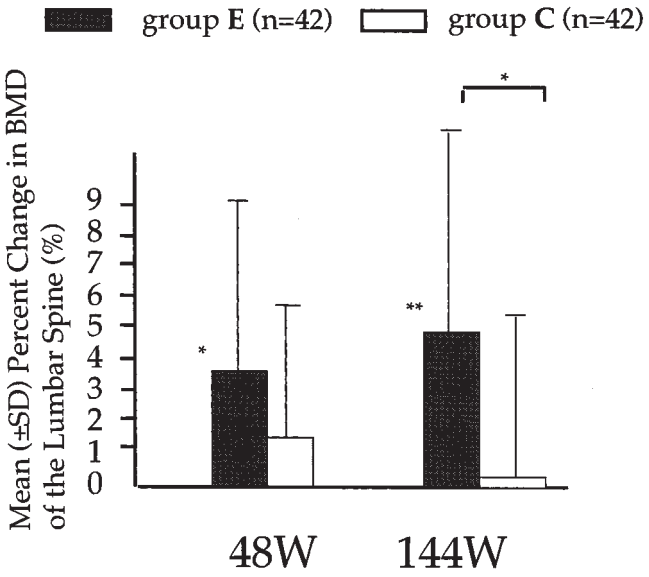

Figure 1. The mean (± SD) percentage change in BMD of the lumbar spine between baseline (0 week) and 48 and 144 weeks of Groups E and C. In all patients, the mean (± SD) percentage change in BMD of the lumbar spine increased from baseline at 48 weeks and 144 weeks in Group E ($p < 0.01$, $p < 0.005$, respectively). The improvement of BMD in Group E was significantly greater than in Group C at 144 weeks ($p < 0.01$). *$p < 0.01$, **$p < 0.005$.

Patients taking corticosteroid therapy had various underlying disorders. In analysis of subgroups based on underlying disease, there was no significant difference between groups in mean percentage change in BMD of lumbar spine (data not shown).

The change in BMD of the lumbar spine between baseline and 48 and 144 weeks of the female patients diagnosed with osteoporosis or osteopenia was compared between Group E and Group C. Thirteen of 15 (87%) patients with osteoporosis or osteopenia in Group E showed an increase in BMD of the lumbar spine at 144 weeks. In contrast, 7 of 12 (58%) patients with osteoporosis or osteopenia in Group C showed a decrease. The rate of increase of BMD in Group C was lower than in Group E.

The baseline values for serum and urine markers of bone turnover were similar in the 2 treatment groups (Figure 3). The baseline concentration of BAP was 108 ± 33 IU/l in Group E and 111 ± 57 IU/l in Group C. It had decreased significantly, 22.8% ($p < 0.01$) in Group E and 23.6% in Group C ($p < 0.05$), at 24 weeks. The difference between investigational groups was not significant. The urinary Dpd value was 6.2 ± 2.4 nM/mM Cr in Group E and 6.3 ± 3.1 nM/mM Cr in Group C at baseline. It decreased 11.1% (NS) in Group E and 3.2% (NS) in Group C at 24 weeks from baseline. The difference between investigational groups was not significant.

Five patients (13%) in Group E and 4 (10%) in Group C had vertebral fractures at baseline; and 2 patients in Group C had a total of 3 new vertebral fractures during the study (Table 2). No patient in Group E had new fractures, but the difference between the groups was not statistically significant. The 2 postmenopausal women in Group C had new vertebral fractures at 144 weeks. One patient in Group C had 2 vertebral fractures. Two patients in Group C who had new vertebral fractures showed a decrease of lumbar spine BMD at 48 weeks and 144 weeks. On radiograph, one patient (Case 1) showed new compression fractures in the 6th and 8th thoracic vertebrae and another (Case 2) had a 12th thoracic vertebral fracture (Figure 4).

Two patients in Group E had adverse events: one had a headache and the other developed a facial rash. Although these events were not considered drug related, patients withdrew from the study for their own safety. No patient had gastrointestinal (GI) side effects.

DISCUSSION

We showed that intermittent cyclical etidronate therapy increases the BMD of lumbar spine induced by corticosteroid in Japanese patients with connective tissue diseases.

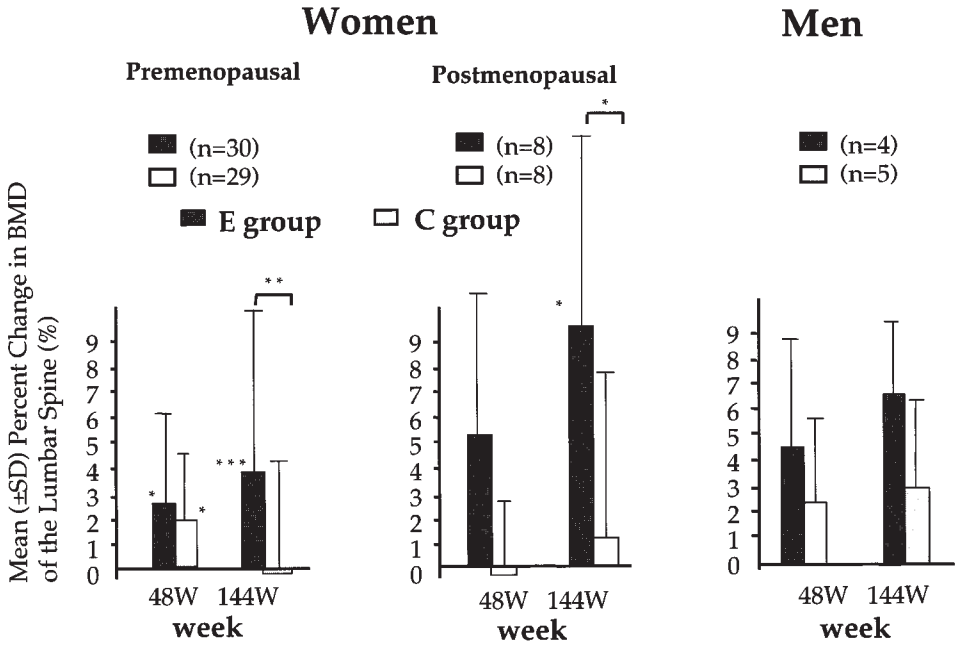

Figure 2. The mean (± SD) percentage change in BMD of the lumbar spine in analysis of subgroups (premenopausal women, postmenopausal women, men). The postmenopausal women of Group E showed the greatest improvement in mean percentage change of lumbar spine BMD at 144 weeks. *p < 0.05, **p < 0.01, ***p < 0.005.

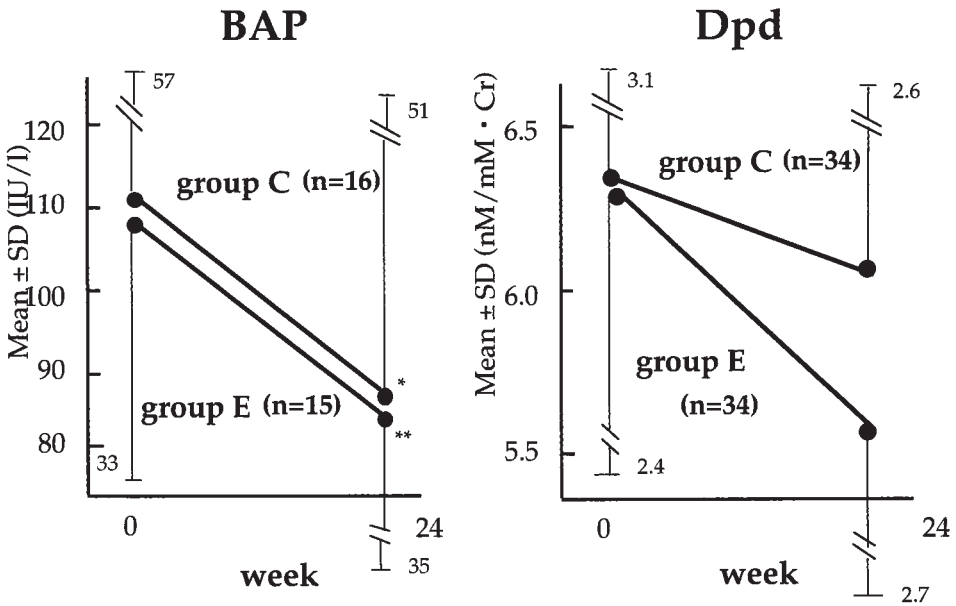

Figure 3. The change (mean ± SD) of serum bone-specific alkaline phosphatase (BAP, left) and urinary deoxypyridinoline (Dpd, right) between baseline and 24 weeks. The mean (± SD) percentage change in serum BAP concentration was significantly decreased at 24 weeks in Group E (p < 0.01). *p < 0.05, **p < 0.01.

A reduction of vertebral fractures was observed, but this did not reach statistical significance.

When we compared the lumbar spine BMD at baseline in 88 women enrolled in the study to the average of age matched normal individuals, 71 (81%) were below the average. In particular, among women younger than 40 years of age, 6 out of 30 (20%) met the criteria for osteoporosis and 10 (33%) met the criteria for osteopenia. These findings suggest that the decrease in BMD was mainly due to the corticosteroid therapy in patients with connective tissue diseases. Because such cases are thought to have a greater risk of future fractures, urgent intervention is required.

Table 2. Incidence of vertebral fractures. Data are number of patients with new vertebral fractures/number of patients who could be evaluated.

	Group E, n = 30	Group C, n = 31
Men	0/3	0/5
Women		
Premenopausal	0/20	0/18
Postmenopausal	0/7	2/8
Total no. of vertebrae fractured	0	3

Bisphosphonates are analogs of inorganic pyrophosphate that inhibit osteoclastic activity, potentially resulting in improved BMD. Etidronate, a first-generation bisphosphonate, has been widely used in various metabolic bone diseases, including Paget's disease of bone[18], hypercalcemia due to malignancy[19], and osteoporosis. It has been reported that etidronate increases the BMD in senile osteoporosis, postmenopausal osteoporosis, and corticosteroid induced osteoporosis[1-7,10,11,13,20,21].

Continuous etidronate therapy has been shown to lead to a mineralization defect in bone, and only inhibits the decrease in BMD and does not produce a distinct increase in BMD. Therefore, it has been suggested that intermittent cyclical etidronate therapy is more effective. A randomized, double-blind, multicenter study to determine the ability of intermittent cyclical etidronate therapy in Japanese patients with involutional osteoporosis[20] indicated prevention and treatment efficacy in both groups that received 200 mg and 400 mg of etidronate. The current approved dose of intermittent cyclical etidronate for treatment of osteoporosis is 200 mg daily in Japan. For this reason, we chose intermittent cyclical therapy, 200 mg of etidronate for 2 weeks with 3.0 g calcium lactate and 0.75 µg alphacalcidol daily for 10 weeks. For ethical purposes, we used 3.0 g calcium lactate and 0.75 µg alphacalcidol daily instead of placebo for our control group. As studies have shown, 0.75 to 1.0 µg alphacalcidol daily was effective in maintaining BMD in patients with osteoporosis compared with placebo[22].

Several randomized and nonrandomized trials have indicated that intermittent cyclical etidronate therapy improved the decrease in BMD in patients with corticosteroid induced osteoporosis[1-7,10,11,13,20,21,23]. Our study is consistent with these findings and demonstrated that etidronate is effective in Japanese patients with corticosteroid induced osteoporosis, as well as in Caucasians. Moreover, this is the first comprehensive study of the efficacy of etidronate 200 mg taken cyclically for 3 years in Japanese patients with corticosteroid induced bone loss.

In our study, the mean (± SD) percentage change in BMD of the lumbar spine increased in Group C at 48 weeks and 144 weeks. This result is significant, as it may show the effect of activated vitamin D_3 in patients with corticosteroid induced osteoporosis, although further longterm observation is needed as the mean percentage change of BMD decreased at 144 weeks compared to 48 weeks in Group C.

Recently, there has been increasing interest in activated vitamin D therapy as monotherapy for corticosteroid induced osteoporosis[24-27]. However, the combination therapy of activated vitamin D with etidronate seemed to be useful because this therapy will minimize the capacity for stimulating bone resorption, while leaving the beneficial effects on intestinal calcium absorption intact. Some reports describe that the combination of activated vitamin D with

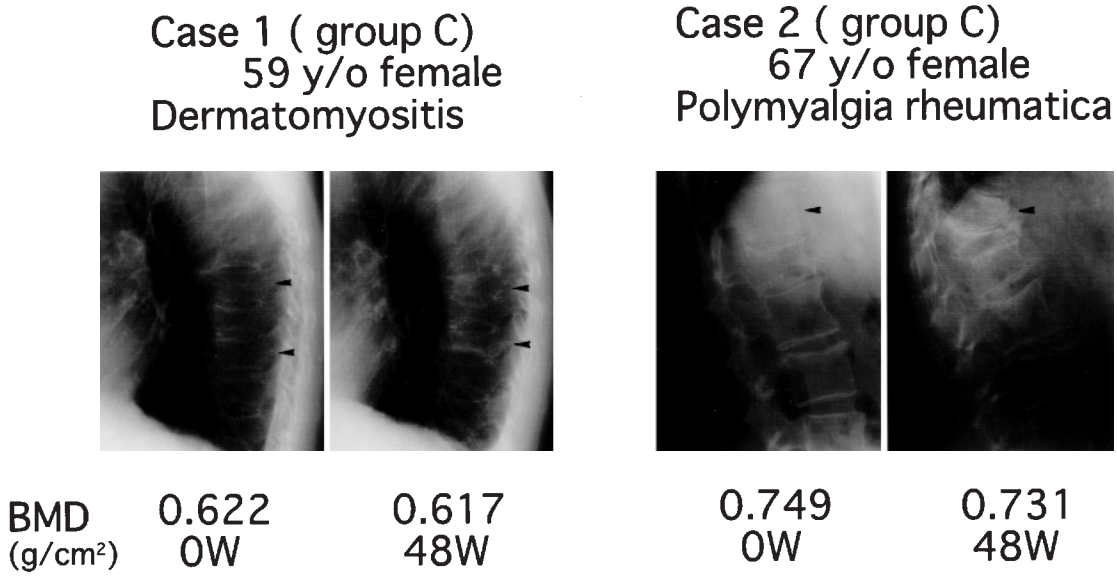

Figure 4. Radiographic change in 2 patients in Group C who had new vertebral compression fractures: in Case 1 in 6th and 8th thoracic vertebrae; in Case 2 in 12th thoracic vertebra.

bisphosphonate is better than bisphosphonate alone[23]. Our results support the combination therapy of activated vitamin D with etidronate as more effective for corticosteroid induced osteoporosis than monotherapy with activated vitamin D preparations.

In analysis of our subgroups, the groups of postmenopausal women and those with osteoporosis + osteopenia of Group E showed the greatest improvement in mean percentage change of BMD. Although the greatest increases in BMD occurring in the osteoporosis + osteopenia subgroup may be accounted for in part by the fact that their baseline BMD is lower, there was a significant increase in bone turnover, as bone absorption was very fast in these groups; and the inhibitory effect of etidronate on bone resorption would correct the bone turnover in a greater degree, causing an increase of BMD. A comparison of BMD in female patients with osteoporosis or osteopenia between Group E and Group C showed an increase in lumbar spine BMD in Group E.

Markers of bone turnover, such as serum BAP and urinary Dpd, were decreased at 24 weeks and correlated with previous reports of intermittent cyclical etidronate therapy[3,5,13]. The change of the urinary Dpd value was of lesser magnitude in Group C than in Group E, and it was thought that the effect of inhibition on bone turnover was mild in Group C.

It was notable that no new vertebral fractures were seen in Group E, although the number of patients was very limited, and there was no significant difference in this respect between groups E and C. The patients who had new vertebral fractures in Group C showed a decrease in lumbar spine BMD at 48 and 144 weeks, suggesting some correlation between the decrease of BMD and the incidence of vertebral fractures.

The trend towards reduction in the incidence of vertebral fractures in this study is comparable with that previously seen[3,10,20] for etidronate therapy in corticosteroid induced osteoporosis and greater than that seen[16,20] in the prevention of vertebral fractures with vitamin D therapy alone. The frequency of vertebral fractures was low in Group C compared to that of placebo groups in previous studies[3,10], and there might be the possibility of the effect to prevent vertebral fractures of lumbar spine occurring in Group C in our study.

We chose to administer a 200 mg daily dose of etidronate. Etidronate caused few adverse effects. In Group E, the headache and facial rash were improved when the patients discontinued etidronate. No upper GI symptoms were experienced by either group. The incidence rate of upper GI events was thought to be dose-dependent[20] and the incidence of upper GI adverse experiences seemed to be low with patients receiving 200 mg etidronate. However, further study will be required to compare the differences in the effect of the prevention of lumbar spine bone loss and vertebral fracture and in the frequency of adverse events between etidronate 200 mg daily and 400 mg daily.

In conclusion, the intermittent administration of etidronate in patients taking corticosteroids significantly increased BMD of the lumbar spine, especially for postmenopausal women and patients with osteoporosis + osteopenia, and the increase was maintained over 3 years. There was a nonstatistically significant reduction in the incidence of vertebral fractures at 3 years between the control and etidronate groups, and no patient in the etidronate group had new fractures. Thus intermittent cyclical etidronate therapy was effective and safe for the prevention and treatment of corticosteroid induced osteoporosis in Japanese patients with connective tissue diseases.

REFERENCES

1. Diamond T, McGuigan L, Barbagallo S, Bryant C. Cyclical etidronate plus ergocalciferol prevents glucocorticoid-induced bone loss in postmenopausal women. Am J Med 1995;98:459-63.
2. Struys A, Snelder AA, Mulder H. Cyclical etidronate reverses bone loss of the spine and proximal femur in patients with established corticosteroid-induced osteoporosis. Am J Med 1995;99:235-42.
3. Adachi JD, Bensen WG, Brown J, et al. Intermittent etidronate therapy to prevent corticosteroid-induced osteoporosis. N Engl J Med 1997;337:382-7.
4. Roux C, Oriente P, Laan R, et al. Randomized trial of effect of cyclical etidronate in the prevention of corticosteroid-induced bone loss. J Clin Endocrinol Metab 1998;83:1128-33.
5. Saag KG, Emkey R, Schnitzer TJ, et al. Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis. N Engl J Med 1998;339:292-9.
6. Adachi JD, Bensen WG, Bianchi F, et al. Vitamin D and calcium in the prevention of corticosteroid induced osteoporosis: a 3 year followup. J Rheumatol 1996;23:995-1000.
7. Pitt P, Li F, Todd P, et al. A double blind placebo controlled study to determine the effects of intermittent cyclical etidronate on bone mineral density in patients on long term oral corticosteroid treatment. Thorax 1998;53:351-6.
8. Reginster JY, Kuntz D, Verdickt W, et al. Prophylactic use of alfacalcidol in corticosteroid-induced osteoporosis. Osteoporos Int 1999;9:75-81.
9. Sambrook P, Birmingham J, Kelly P, et al. Prevention of corticosteroid osteoporosis. A comparison of calcium, calcitriol, and calcitonin. N Engl J Med 1993;328:1747-52.
10. Sebaldt RJ, Ioannidis G, Adachi JD, et al. 36 month intermittent cyclical etidronate treatment in patients with established corticosteroid induced osteoporosis. J Rheumatol 1999;26:1545-9.
11. Homik JE, Cranney A, Shea B, et al. A metaanalysis on the use of bisphosphonates in corticosteroid induced osteoporosis. J Rheumatol 1999;26:1148-57.
12. Shiraki M, Shiraki Y, Aoki C, Miura M. Vitamin K_2 (menatetrenone) effectively prevents fractures and sustains lumbar bone mineral density in osteoporosis. J Bone Miner Res 2000;15:515-21.
13. Adachi JD, Saag KG, Delmas PD, et al. Two-year effects of alendronate on bone mineral density and vertebral fracture in patients receiving glucocorticoids: a randomized, double-blind, placebo-controlled extension trial. Arthritis Rheum 2001;44:202-11.
14. Dougherty JA. Risedronate for the prevention and treatment of corticosteroid-induced osteoporosis. Ann Pharmacother 2002;36:512-6.
15. Reid DM, Adami S, Devogelaer JP, Chines AA. Risedronate increases bone density and reduces vertebral fracture risk within one

year in men on corticosteroid therapy. Calcif Tissue Int 2001;69:242-7.
16. Kushida K, Shiraki M, Nakamura T, et al. The efficacy of alendronate in reducing the risk for vertebral fracture in Japanese patients with osteoporosis: a randomized, double-blind, active-controlled, double-dummy trial. Curr Ther Res Clin Exp 2002;63:606-20.
17. Orimo H, Sugioka Y, Fukunaga H, et al. Diagnostic criteria for primary osteoporosis recommended by the Japanese Society of Bone and Mineral Research in 1996. Osteoporosis Japan 1996;4:65-75.
18. Alexandre C, Meunier PJ, Edouard C, Khairi RA, Johnston CC. Effects of ethane-1 hydroxy-1, 1-diphosphonate (5 mg/kg/day dose) on quantitative bone histology in Paget's disease of bone. Metab Bone Dis Relat Res 1981;3:309-15.
19. Fleisch H. Bisphosphonates. Pharmacology and use in the treatment of tumor-induced hypercalcaemic and metastatic bone disease. Drugs 1991;42:919-44.
20. Fujita T, Orimo H, Inoue T, et al. Double-blind multicenter comparative study with alfacalcidol of etidronate disodium (EHDP) in involutional osteoporosis. Clin Eval 1993;21:261-302.
21. Miller PD, Watts NB, Licata AA, et al. Cyclical etidronate in the treatment of postmenopausal osteoporosis: efficacy and safety after seven years of treatment. Am J Med 1997;103:468-76.
22. Orimo H, Shiraki M, Hayashi T, Nakamura T. Reduced occurrence of vertebral crush fractures in senile osteoporosis treated with 1 alpha (OH)-vitamin D3. Bone Miner 1987;3:47-52.
23. Masud T, Mulcahy B, Thompson AV, et al. Effects of cyclical etidronate combined with calcitriol versus cyclical etidronate alone on spine and femoral neck bone mineral density in postmenopausal osteoporotic women. Ann Rheum Dis 1998:57;346-9.
24. Shiraki M, Kushida K, Yamazaki K, et al. Effects of 2 years treatment of osteoporosis with 1-alpha-hydroxy vitamin D3 on bone mineral density and incidence of fracture—a placebo-controlled, double-blind prospective study. Endocrine J 1996;43:211-20.
25. Chen JT, Shiraki M, Hasumi K, et al. 1-alpha-hydroxyvitamin D3 treatment decreases bone turnover and modulates calcium-regulating hormones in early postmenopausal women. Bone 1997:20:557-62.
26. Shiraki M, Kushida K, Fukunaga M, et al. A double-masked multicenter comparative study between alendronate and alfacalcidol in Japanese patients with osteoporosis. The Alendronate Phase III Osteoporosis Treatment Research Group. Osteoporos Int 1999;10:183-92.
27. Lakatos P, Nagy Z, Kiss L, et al. Prevention of corticosteroid-induced osteoporosis by alfacalcidol. Z Rheumatol 2000;59 Suppl 1:48-52.