Allergology International. 2005;54:137-141

ORIGINAL ARTICLE

Improvement of Reduced Bone Mineral Density by Intermittent Cyclical Etidronate in Postmenopausal Asthmatic Patients Receiving Inhaled Corticosteroids

Hiroyasu Yamamoto[1], Soji Kasayama[1], Mari Fujita[2], Kimie Fujita[3], Yasuhiko Morimoto[4], Ichiro Kawase[1] and Akihiko Miyatake[5]

ABSTRACT

Background: We have recently shown that early postmenopausal but not premenopausal asthmatic women treated with inhaled corticosteroids demonstrate reduced bone mineral density(BMD)and decreased serum intact osteocalcin levels. Thus, the development of therapeutic approaches would be desirable for the prevention and intervention of BMD reduction in postmenopausal asthmatic women receiving inhaled corticosteroids.

Methods: This study was aimed at examining the effects of etidronate disodium on BMD in 20 postmenopausal asthmatic women with reduced BMD of the lumbar spine(T score ; −1.5 or less). These patients had been managed by inhaled beclomethasone dipropionate or inhaled fluticasone propionate, without regular use of oral or parentheral corticosteroids. They were given a 200 mg/day oral dose of etidronate disodium for 14 days every three months. BMD of the lumbar spine was determined at baseline and at 1 or 3 years after the treatment.

Results: The baseline BMD was 0.692±0.018(SE)g/cm^2(T score, −3.0±0.8). The BMD significantly increased by 5.2±2.0% at 1 year(*P*=0.022)and by 7.3±2.9% at 3 years(*P*=0.037)after the treatment.

Conclusions: Intermittent cyclical treatment with ethidronate improves reduced BMD in postmenopausal asthmatic women on inhaled corticosteroid therapy.

KEY WORDS

bisphosphonate, bronchial asthma, inhaled corticosteroids, osteoporosis, postmenopausal women

INTRODUCTION

Inhaled corticosteroids are now the mainstay for long-term treatment of bronchial asthma.[1] Although systemic use of corticosteroids is a well-known risk for osteoporosis, it has remained undetermined as to whether long-term use of inhaled corticosteroids can cause osteoporosis.[2,3] Inconsistent conclusions drawn from previous studies on the effects of inhaled corticosteroids on bone are probably due to the differences in clinical characteristics of the study patients with regard to sex, age, menstrual status, and co-administration of systemic corticosteroids.[4-10] In this regard, we previously analyzed bone mineral density (BMD) and biochemical markers of bone metabolism in pre- and early post-menopausal asthmatic women treated with inhaled beclomethasone propionate but without oral or parentheral administration of corticosteroids for at least 1 year. Our results showed that inhaled corticosteroids have unfavorable effects on bone in postmenopausal but not in premenopausal asthmatics.[11] Therefore, it can be postlated that thera-

[1]Department of Molecular Medicine, Osaka University Graduate School of Medicine, [4]Department of Internal Medicine, Aizenbashi Hospital, [5]Miyatake Asthma Clinic, Osaka, [2]Kyoto Prefectural University of Medicine, Kyoto and [3]University of Shiga Prefecture, Shiga, Japan.
Correspondence: Professor Akihiko Miyatake, Miyatake Asthma Clinic, 10F 2−2−3 Dai-San-Shoho Building, Nishi-Shinsaibashi, Chuo-ku, Osaka 542−0086, Japan.
Email: akihiko@skyblue.ocn.ne.jp
Received 6 May 2004. Accepted for publication 22 July 2004.

Table 1 Characteristics of etidronate-treated postmenopausal asthmatic women

Number	*20*	
Age	69.7±1.1	(60–78)
Years after menopause (year)	19.2±1.7	(4–34)
Asthma status (step 2/3/4)*	11/9/0	
Dose of inhaled corticosteroids (μg/day)**	647±52	(118–1034)
BMD of lumbar spine (L2-L4) (g/cm^2)	0.692±0.018	(0.531–0.795)
BMD of lumbar spine (L2-L4) (T-score)	− 3.0±0.8	(− 4.3–− 2.0)

Data are means±SE or *n.* Ranges are shown in parenthesis. *Asthma status is according to NHLBI/WHO (1995) classification. **Dose of inhaled corticosteroids is expressed as that of beclomethasone. Dose of fluticasone is multiplied by 2 for the conversion.

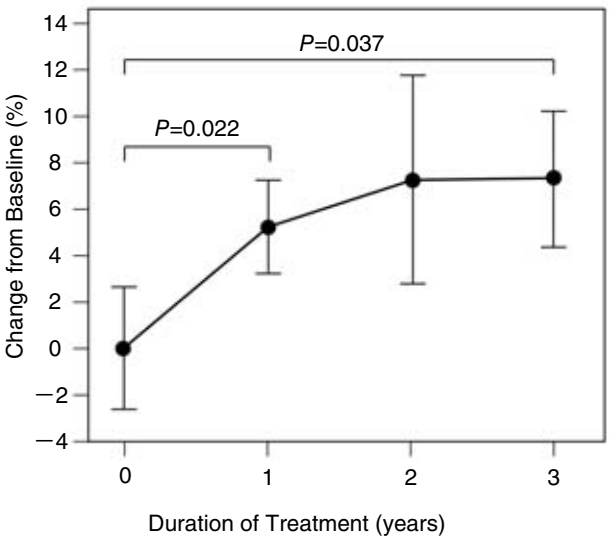

Fig. 1 Changes of lumbar spinal BMD in 20 postmenopausal asthmatic patients receiving inhaled corticosteroids before and after treatment with intermittent cyclical etidronate. Data represent mean ±SE.

peutic approaches would be necessary for the prevention and intervention of BMD reduction in inhaled corticosteroids-treated postmenopausal patients.

Bisphosphonates are potent inhibitors of bone resorption mediated by osteoclasts both *in vitro* and *in vivo*. Several treatments using these agents as well as ovarian hormones have been shown effective in preventing bone loss and vertebral fracture in patients who were given systemic corticosteroids.[12-16] However, strategies for the prevention of bone loss in patients with use of inhaled corticosteroids are not yet confirmed. In the present study, we evaluated the therapeutic benefit of intermittent cyclical therapy of etidronate for reduction of bone loss in postmenopausal asthmatic patients receiving inhaled corticosteroids.

METHODS

EXPERIMENTAL SUBJECTS

Among 784 Japanese female patients who were diagnosed with bronchial asthma at the Miyatake Asthma Clinic by the American Thoracic Society criteria,[17] we randomly recruited 20 postmenopausal women satisfying the following admission criteria : no continuous use of oral corticosteroid therapy ; no histry of estrogens or progestins use ; no endocrine, metabolic or renal disorders ; no lumbar spinal deformities ; no bone fractures ; and a lumbar spine BMD T score of −1.5 or less. None of the women had a history of smoking. All patients were fully ambulatory and their ADLs were normal. They were managed by inhaled beclomethasone dipropionate or inhaled fluticasone propionate, and disodium cromoglycate, β-stimulants, and/or theophylline. All the patients properly used a metered-dose inhaler with a spacer (Volumatic ; Glaxo SmithKline , Middlesex , UK , or Inspire-Ease ; Schering-Plough, Kenilworth, NJ). In 12 patients who had been taking alfacalcidol (1.0 μg/day), the administration continued throughout the study period. They were managed by the same physician (A. M.) in the outpatient clinic every 2 or 4 weeks.

STUDY DESIGN

All patients in the study were treated with intermittent cyclical etidronate (Sumitomo Pharmaceutical, Osaka, Japan). They were administered etidronate disodium 200 mg/day for 14 days for every 3-month period. During the study period, some of the patients received oral or parenteral administration of corticosteroids for short time for the treatment of asthma attack. BMD was measured at the lumbar spine (L2-L4) level using the dual-energy X-ray absorptiometry (DXA) technique at baseline and at 1, 2 or 3 years after the administration of etidronate. The protocol in this study was approved by the regional ethical committee, and all the patients provided informed consent.

BMD MEASUREMENTS

BMD was measured with DXA scans (Hologic QDR-2000, Waltham, MA). The measurement was performed by the same technician who was not informed about the clinical status of the patient.

STATISTICAL ANALYSIS

All results are shown as means±SE. Data were compared using analysis of variance and by paired *t* -test. Differences associated with $P<0.05$ were considered statistically significant.

RESULTS

Clinical characteristics of the twenty postmenopausal women with bronchial asthma at entry of the study are shown in Table 1. Age of the study patients was 69.7±1.1 years and 19.2±1.7 years from after the time menopause. The dose of inhaled corticosteroids was 647±52 μg/day of beclomethasone. All patients were diagnosed as step 2 or step 3 asthma statuses, according to NHLBI/WHO (1995) classification. Their baseline lumber spine (L2-L4) BMD was 0.692±0.018 g/cm ^{2} (T score −3.0±0.8 ; −4.3～−2.0). Twelve patients (60%) had BMD T score of −2.5 or less, which was operationally defined as osteoporosis by the World Health Organization.[18] Changes in the lumbar BMD are shown in Figure 1. At 1 year after etidronate treatment, BMD significantly increased by 5.2±2.0% (n=11, P=0.022). After 3 years of treatment, there were significant increases by 7.3±2.9% from baseline (n=12, P=0.037). In patients with alfacalcidol BMD changes at 1 year and at 3 years were 6.1±3.1% (n=7) and 11.3±4.3% (n=7), whereas those were 3.6±1.7% (n=4) and 1.7±1.2% (n=5) in patients without alfacalcidol. There was no statistically significant difference between the both groups. None of the study patients had esophageal or gastrointestinal complaints during the study period. Laboratory examinations revealed no abnormalities of hepatic or renal function.

DISCUSSION

There has been some controversy concerning the effects of inhaled corticosteroids on bone density and fractures in asthmatic patients.[4-10] A recent study[19] showed a negative correlation between total cumulative dose of inhaled corticosteroids and BMD in asthmatic men and women aged 20−40 years. A large scale of study using a data base of patients of averaging age 45 years of age[20] has shown that users of inhaled corticosteroid have an increased risk of bone fracture but this excess risk may be more related to the underlying respiratory disease than to inhaled corticosteroids. Reduced respiratory function is also shown to be associated with spinal deformity[21] as well as low BMD.[22] Thus, many variables, such as age, sex, menstrual status, respiratory function and use of systemic corticosteroids, should be considered in the analysis of the involvement of inhaled corticosteroids in osteoporosis and the effects of various drugs on its prevention. We have recently shown that inhaled corticosteroids reduce BMD in early postmenopausal but not in premenopausal asthmatic women.[11] From these observations, we thought that it is important to find therapeutic modalities for treating bone loss in postmenopausal asthmatic patients receiving inhaled corticosteroids.

In this investigation, intermittent cyclical administration of etidronate was found to increase BMD in 20 postmenopausal asthmatic women. A statistically significant increment was evident at 1 year as well as 3 years after the treatment. Control patients without etidronate treatment were not evaluated in this study. However, it is known that postmenopausal elderly women show no significant increase in BMD. Thus, the results of the present study indicate the efficacy of the intermittent cyclical etidronate treatment for increasing BMD in postmenopausal asthmatic women receiving inhaled corticosteroids. The increases in BMD (5.2±2.0% at 1 year and 7.3±2.9% at 3 years) corresponded to those obtained by effective treatment with antiresorptive drugs in postmenopausal women (5−10% in 2 years), which were associated with a decrease in the fracture rate of approximately 50%.[23]

It has been recently shown that the other bisphosphonate alendronate treatments increased BMD in patients on inhaled corticosteroid therapy.[24] This recent study included patients with bronchial asthma as well as those with chronic obstructive airway diseases. About half of the study patients were premenopausal and some patients were on oral corticosteroids. In addition, only 10% had BMD T scores less than −2.5. By contrast, in the present investigation, we focused on postmenopausal asthmatic women without continuous use of oral corticosteroids in whom BMD T scores were −1.5 or less, which is the threshold for treatment by National Osteoporosis Foundation criteria.[25] Average BMD T score was −3.0 (range ; −4.3 to −2.0). Sixty % of the study patients had a BMD T score −2.5 or less and thus they were diagnosed with osteoporosis based on the definition by a working group of the World Health Organization.[18] Therefore, our study is the first to demonstrate the effectiveness of the use of bisphosphonate for reducing BMD in postmenopausal asthmatic women who were treated with inhaled corticosteroids but no continuous use of systemic corticosteroids.

Twelve patients had been taking alfacalcidol before entry of this study and continued to receive it throughout the study period, whereas the other 8 patients did not. BMD changes had a tendency to be slightly higher in patients taking alfacalcidol, but there was no statistically significant difference of BMD changes between both groups. It remains to be determined whether alfacalcidol has an additive effect on the action of bisphosphonates to increase BMD in postmenopausal osteoporosis. Thus, further study will be also needed to clarify the effects of coadministration of cyclical etidronate and alfacalcidol on bone metabolism in asthmatic women with inhaled corticosteroids.

Our previous study[11] has revealed that serum intact osteocalcin concentration was depressed in post-

menopausal asthmatics receiving corticosteroids compared with postmenopausal control subjects. By contrast, urinary pyridinoline and deoxypyridinoline concentrations did not differ between the postmenopausal asthmatics and the postmenopausal control subjects. These results indicate that inhaled corticosteroids cause reduced bone formation rather than increased bone resorption. Therefore, approaches to increase bone formation would ideally be desirable for the treatment of bone loss in postmenopausal asthmatic women. Since the main mechanism of action of etidronate is interference with osteoclast function and inhibition of bone resorption, the reason for its effectiveness on the bone loss in inhaled corticosteroids-treated postmenopausal asthmatic women seems unclear. In this study, we did not determine biochemical markers of bone metabolism before and after the etidronate treatment. It has been shown that etidronate prevented bone loss in patients with systemic corticosteroid therapy in whom it decreased levels of the bone resorption marker urinary pyridinium as well as of the bone formation marker osteocalcin.[15] Taken all together, the inhibitory effects of etidronate on bone resorption in postmenopausal state may surpass the inhibition of bone formation by inhaled corticosteroids.

In conclusion, we found that intermittent cyclical etidronate therapy was effective in the treatment of bone loss in postmenopausal asthmatic patients receiving inhaled corticosteroids. Since wide use of inhaled corticosteroids is now associated with decreased mortality of asthmatic patients,[26] the prevention of osteoporosis and osteoporotic fracture will be important in the consideration of health problems in asthmatic women treated with inhaled corticosteroids.

ACKNOWLEDGEMENTS

We thank Mr. Yoshio Matsumoto at Aizenbashi Hospital for helping the measurement of BMD. We also thank Miss Miho Sasaki for her secretarial assistance.

REFERENCES

1. The British Thoracic Society . Guidelines on the management of asthma. *Thorax* 1998;**48**(2 Suppl):S1-24.
2. Barnes PJ, Pedersen S, Busse WW. Efficacy and safety of inhaled corticosteroids. New development. *Am. J. Resp. Crit. Care Med.* 1998;**157**(3 Pt 2):S1-53.
3. Efthimiou J, Barnes PJ. Effect of inhaled corticosteroids on bone and growth. *Eur. Respir. J.* 1998;**11**:1167-1177.
4. Kerstjens HAM, Postma DS, van Doormaal JJ *et al*. Effects of short-term and long-term treatment with inhaled corticosteroids on bone metabolism in patients with airways obstruction. Dutch CNSLD Study Group. *Thorax* 1994;**49**:652-656.
5. Ip M, Lam K, Yam L, Kung A, Ng M. Decreased bone mineral density in premenopausal asthmatic patients receiving long-term inhaled steroids. *Chest* 1994;**105**:1722-1727.
6. Herrala J, Puolijoki H, Impivaara O, Liippo K, Tala E, Nieminen MM. Bone mineral density in asthmatic women on high-dose inhaled beclomethasone dipropionate. *Bone* 1994;**15**:621-623.
7. Nagasaka Y, Fujita E, Okawa K *et al*. Effect of inhaled steroid on bone metabolism in the treatment of bronchial asthma. *Arerugi* 1994;**43**:1398-1404(in Japanese).
8. Toogood JH, Baskerville JC, Markov AE *et al*. Bone mineral density and risk of fracture in patients receiving long-term inhaled steroid therapy for asthma. *J. Allergy Clin. Immunol.* 1995;**96**:157-166(in Japanese).
9. Hanania NA, Chapman KR, Sturgridge WC, Szalai JP, Kesten S. Dose-related decrease in bone density among asthmatic patients with inhaled corticosteroids. *J. Allergy Clin. Immunol.* 1995;**96**:571-579.
10. Packe GE, Robb O, Robins SP, Reid DM, Douglas JG. Bone density in asthmatic patients taking inhaled corticosteroids : Comparison of budesonide and beclomethasone dipropinate. *J. R. Coll. Physicians Lond.* 1996;**30**:128-132.
11. Fujita K, Kasayama S, Hashimoto J *et al*. Inhaled corticosteroids reduce bone mineral density in early postmenopausal but not premenopausal asthmatic women. *J. Bone Miner. Res.* 2001;**16**:782-787.
12. Lukert BP, Johnson BE, Robinson RG. Estrogen and progesterone replacement therapy reduces glucocorticoid-induced bone loss. *J. Bone Miner. Res.* 1992;**7**:1063-1069.
13. Struys A, Snelder AA, Mulder H. Cyclical etidronate reverse bone loss of the spine and proximal femur in patients with established corticosteroid-induced osteoporosis. *Am. J. Med.* 1995;**99**:235-242.
14. Adachi JD, Bensen WG, Brown J *et al*. Intermittent etidronate therapy to prevent corticosteroid-induced osteoporosis. *N. Engl. J. Med.* 1997;**337**:382-387.
15. 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**:1128-1133.
16. 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**:202-211.
17. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. *Am. Rev. Respir. Dis.* 1987;**136**:225-244.
18. Kanis JA, Melton LJ III , Chrstiansen S *et al*. The diagnosis of osteoporosis. *J. Bone Miner. Res.* 1994;**9**:1137-1141.
19. Wong CA, Walsh LJ, Smith CJ *et al*. Inhaled corticosteroid use and bone-mineral density in patients with asthma. *Lancet* 2000;**355**:1399-1403.
20. Van Staa TP, Leufkens HGM, Cooper C. Use of inhaled corticosteroids and risk of fractures. *J. Bone Miner. Res.* 2001;**16**:581-588.
21. Schlaich C, Minne HW, Bruckner T *et al*. Reduced pulmonary function in patients with spinal osteoporotic fractures. *Osteoporos. Int.* 1998;**8**:261-267.
22. Lekamwasam S, Trivedi DP, Khaw KT. An association between respiratory function and bone mineral density in women from the general community : A cross sectional

study. *Osteoporos. Int.* 2002;**13**:710-715.

23. Eastell R. Treatment of postmenopausal osteoporosis. *N. Engl. J. Med.* 1998;**338**:736-746.

24. Lau EM, Woo J, Chan YH, Li M. Alendronate for the prevention of bone loss in patients on inhaled steroid therapy. *Bone* 2001;**29**:506-510.

25. National Osteoporosis Foundation . Osteoporosis : review of the evidence for the prevention, diagnosis and treatment and cost-effectiveness analysis. *Osteoporos. Int.* 1998;**8**(Suppl. 4):S1-88.

26. Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. *N. Engl. J. Med.* 2000;**343**:332-336.