—Regular Articles—

Comparative Studies on Effect of Risedronate and Alfacalcidol against Glucocorticoid-Induced Osteoporosis in Rheumatoid Arthritic Patients

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Osteoporosis is a common adverse reaction induced by glucocorticoid treatment. Bisphosphonate, vitamin D_3 (VD_3) or vitamin K_2 (VK_2) is recommended as first or second choice of drug for treatment of glucocorticoid-induced osteoporosis. In the present study, the treatment effect of risedronate against glucocorticoid-induced osteoporosis in rheumatoid arthritic patients was compared with that of alfacalcidol. Twelve patients were randomized to receive either risedronate (2.5 mg) or alfacalcidol (0.5 μg) daily for 48 weeks. Each patient also received 800 mg of calcium supplementation (800 mg/day) daily. Bone mineral density (BMD) and the biochemical markers of bone turnover were measured before (baseline) and 12, 24, and 48 weeks after treatment with risedronate or alfacalcidol, and the percentage changes in these parameters from baseline were compared.The BMD values 12, 24 and 48 weeks after treatment with risedronate increased by 3.9%, 4.1% and 5.2%, respectively, which were significantly higher than those after treatment with alfacalcidol (2.8%, 2.1% and 2.5%, respectively). Urinary excretion of *N*-telopeptides of type I collagen and deoxypyridinoline after risedronate treatment were more significantly decreased than that after alfacalcidol treatment. The present findings at least suggest that risedronate is more useful for the prevention and treatment of glucocorticoid-induced osteoporosis in patients with rheumatoid arthritis than alfacalcidol, although the number of patients studied was small.

Key words——osteoporosis; rheumatoid arthritis; risedronate; vitamin D_3; bone mineral density

INTRODUCTION

Glucocorticoids, which have strong anti-inflammatory and immunosuppressive action, are widely used for the treatment of various diseases, including rheumatoid arthritis, starting collagen disease, bronchial asthma, and nephrosis syndrome. The use of glucocorticoids in the treatment of such diseases causes a variety of adverse reactions, including osteoporosis. It is reported that the use of glucocorticoids is associated with an increased risk for bone loss and fractures in patients with rheumatoid arthritis.[1] It is also reported that a high-dose of glucocorticoids significantly increased the incidence of fractures in postmenopausal patients with rheumatoid arthritis compared to a low-dose.[2] Based on these findings, the importance of glucocorticoid-induced osteoporosis has been widely accepted in many countries.

Guidelines for prevention and treatment of glucocorticoid-induced osteoporosis have recently been developed.[3–6] The guidelines recommend the use of bisphosphonates as a potential therapy for glucocorticoid-induced osteoporosis because of their high ability to inhibit bone resorption and low side effects, although other drugs such as vitamin D and its analogues, and calcitonin have been reported to be effective in the prevention of bone loss. For example, it is well known that commercially available bisphosphonates significantly increase or maintain bone mineral density (BMD) in patients with glucocorticoid-induced osteoporosis. In addition to the measurement of BMD for the diagnosis and monitoring of osteoporosis, the importance of the measurement of bone turnover markers, such as urinary *N*-telopeptides of type I collagen (NTX), urinary deoxypyridinoline (DPD), serum osteocalcin (OC), serum bone-specific alkaline phosphatase (BAP), serum alkaline phosphatase (ALP), serum calcium (Ca), serum inorganic phosphate (P), and serum 1α, 25-dihydroxyvitamin D (1,25[OH]$_2$D), has also become indispensable.[7,8] However, to our knowledge, although there are some studies using

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both BMD and bone turnover markers in comparison to the efficacy of drugs,[9–12] there are few studies using them to prevent or treat osteoporosis in Japanese patients with rheumatoid arthritis and glucocorticoid-induced osteoporosis.

Risedronate, a potent bisphosphonate, is widely used as first choice of drug for the prevention and treatment of glucocorticoid-induced osteoporosis in Japan because it increases BMD and reduces the incidence of spine and hip fractures. On the other hand, alfacalcidol is a synthetic analogue of activated vitamin D_3 and is widely used in combination with calcium in the prevention and treatment of glucocorticoid-induced osteoporosis. In the present study, we compared the protective and treatment effects of risedronate with those of alfacalcidol against glucocorticoid-induced osteoporosis in rheumatoid arthritic patients by measuring BMD and various biochemical markers of bone turnover.

SUBJECTS AND METHODS

Study Design The study was approved by the clinical investigation committee of Nagoya Kyoritsu Hospital. Informed consent was obtained from each patient after full explanation of the objective and procedures of the study. Twelve female rheumatoid arthritic patients with glucocorticoid-induced osteoporosis were randomly divided into two groups (risedronate and alfacalcidol treatment groups). One group of 6 patients received a tablet of risedronate (2.5 mg, Aventis Pharma Japan, Ltd., Tokyo, Japan) once daily in the early morning for 48 weeks. The instructions for taking risedronate were to swallow the tablet with a full glass (180 ml) of plain water (not mineral water, tea, or juice) first thing in the morning on an empty stomach, wait at least 30 min before eating breakfast or taking any other medication, and not lie down until after breakfast. The other group of 6 patients received a tablet of alfacalcidol (0.5 μg, Chugai Pharmaceutical Co. Ltd., Tokyo, Japan) once daily for 48 weeks. All patients also received 800 mg of calcium aspartate per day.

Patient Selection The patients, who were enrolled at Nagoya Kyoritsu Hospital between May 2002 and May 2003, were Japanese who had glucocorticoid-induced osteoporosis consistent with the criteria for diagnosis of osteoporosis in Japan,[13] and an L2–L4 BMD T-score of at least 2.5 standard deviations below the young adult mean,[14] and who were taking glucocorticoid, were not taking any medication that could affect bone or calcium metabolism, and had no past history of bisphosphonate treatment.

Measurements BMD was measured by dual-energy X-ray absorptiometry (DXA) bone densitometry at just before and 12, 24, and 48 weeks using QDR4500A, HOLOGIC, USA. Blood samples were collected at baseline (week 0) and at weeks 12, 24, and 48 in both groups. Morning second-void urine samples were collected at baseline (week 0) and weeks 12, 24, and 48 in both groups. Serum was separated within one hour and stored at -70℃. Urine was stored at -20℃.

The urine levels of NTX and DPD (each measured by enzyme immunoassay and expressed as a ratio to urinary creatinine) were assayed serially before and at 12, 24 and 48 weeks after the initiation of treatment. The serum levels of OC (radioimmunoassay), BAP (measured by enzyme immunoassay), and 1,25(OH)2D (radioimmunoassay) were assayed serially before, and at 12, 24 and 48 weeks after, the initiation of treatment. Ca, P, and ALP were assayed at Nagoya Kyoritsu Hospital and Hoken Kagaku Bio Laboratories (Tokyo, Japan) to detect possible hypercalcemia at the time intervals described above. All the above measurements were carried out at one laboratory (Hoken Kagaku Bio Laboratories, Tokyo) before the treatment code was broken.

Statistical Analysis The baseline characteristics of the patients were compared between the two treatment groups by a two-tailed Student *t*-test. All data are expressed as mean value (SD and were analyzed using a two-tailed Student *t*-test for paired values with a 5% significance level.

RESULTS

General Twelve patients had baseline measurements, and none of them dropped out. No patient experienced any adverse reaction. Table 1 shows the baseline characteristics and results of the two treatment groups. There were no significant differences between the groups, nor were there any clear differences between the two groups in RA treatments by glucocorticoid therapy.

Bone Mineral Density The BMD results over the 48 weeks of the study are shown in Fig. 1. In the risedronate group, BMD had increased by 3.9 ± 6.1 %, 4.1 ± 3.9%, and 5.2 ± 5.2% (mean$\pm$SD), respectively, at 12, 24, and 48 weeks after the initiation of

Table 1. Baseline Characteristics of Patients in This Study

	Risedronate	Alfacalcidol
Age (years)	69.2±6.0	72.0±8.7
Sex (m/f)	0/6	0/6
Height (cm)	153.2±5.3	152.5±6.5
Weight (kg)	48.5±2.3	48.1±1.9
Years post menopause	22.5±3.8	23.4±2.9
Duration of glucocorticoid therapy (month)	33.3±5.7	25.6±12.3
Dosage of glucocorticoid (mg/day)	3.5±1.7	3.5±2.8
LBMD (kg/cm^2)	0.64±0.10	0.64±0.10
NTX (nM/mMCr)	56.1±11.5	55.2±32.7
DPD (nM/mMCr)	7.1±0.4	6.9±1.0
Osteocalcin (ng/ml)	8.6±0.6	8.5±0.6
BAP (ng/ml)	24.0±9.3	26.3±4.6
Serum alkali phosphatase (IU/I)	264.8±82.0	261.6±88.3
Serum calcium (mg/dl)	8.8±0.5	8.7±0.3
Iorganic phosphate (mg/dl)	3.8±0.3	3.9±0.4
1,25-$(OH)_2$ D (pg/ml)	32.5±5.4	32.8±3.6
Other medications (%)		
Methotrexate	66%	50%
Leflunomide	0%	16%
Bucillamine	16%	33%
Salazosulfapyridine	16%	0%

Each value represents mean±S.E. ($n=6$). No significant differences were observed between risedronate and alfacalcidol. LBMD: lumbar bone mineral density, NTX: urinary *N*-telopeptides of type I collagen, DPD: urinary deoxypyridinoline, BAP: serum bone specific alkaline phosphatase, 1,25-$(OH)_2$ D, 1α, 25-dihydroxyvitamin D. The glucocorticoid used for the treatment of RA was prednisolone.

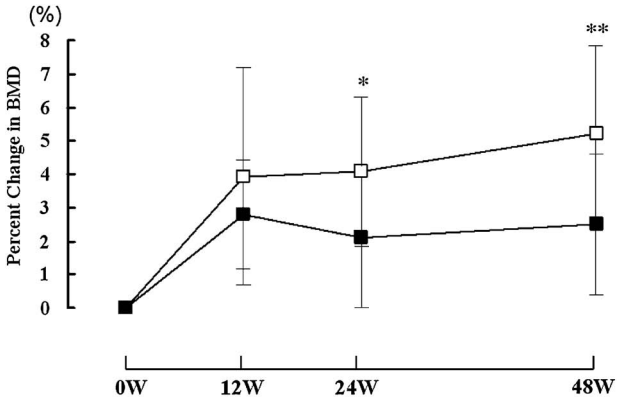

Fig. 1. The Change from Baseline in the BMD for Risedronate (□) and Alfacalcidol (■) Administration after 48 Weeks in Japanese Osteoporosis Patients

Each point represents the mean±S.E. ($n=6$). *=p value of RIS vs. VD_3 (*$p<0.05$, **$p<0.01$).

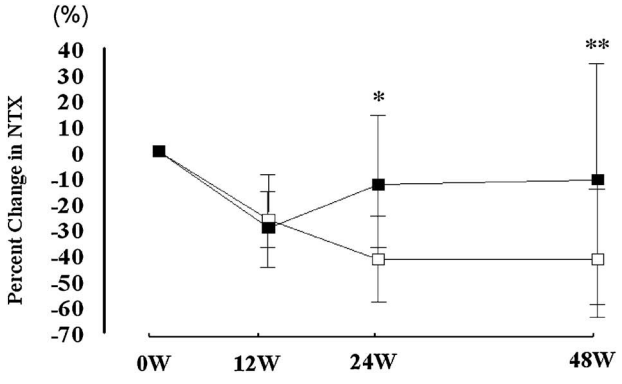

Fig. 2. The Change from Baseline in the Urine NTX for Risedronate (□) and Alfacalcidol (■) Administration after 48 Weeks in Japanese Osteoporosis Patients

Each point represents the mean±S.E. ($n=6$). *=p value of RIS vs. VD_3 (*$p<0.05$, **$p<0.01$).

treatment. Corresponding values in the alfacalcidol group were 2.8±3.1%, 2.1±4.2%, and 2.5±4.1%. There was a significant difference between the two groups at each of the observation time points ($p<0.05$ at week 24, and $p<0.01$ at week 48).

Bone Turnover Markers and Bone Metabolism Parameter The urinary NTX results over the 48 weeks of the study are shown in Fig. 2. In the risedronate group, urinary NTX decreases of −26.2±17.4%, −42.0±29.7% and −42.0±50.4% (mean±SD) were observed, respectively, at 12, 24 and 48 weeks after the initiation of treatment. Correspond-

ing values in the alfacalcidol group were -29.6 ± 25.1 %, -12.8 ± 52.6%, and -10.9 ± 88.5%. There was a significant difference between the two groups at each of the observation time points ($p<0.05$ at week 24, and $p<0.01$ at week 48).

Urinary DPD excretion was decreased by risedronate at week 48 by -48.1 ± 31.6% (Fig. 3). The urinary DPD response to risedronate was seen as early as week 4; however, a urinary DPD response to alfacalcidol was not seen. There was a significant difference between the two groups at each of the observation time points ($p<0.001$ at week 12, $p<0.01$ at week 24, and $p<0.01$ at week 48).

The serum OC and BAP results over the 48 weeks of the study are shown in Figs. 4 and Fig. 5. Although there were no significant differences between the two groups in OC or BAP at week 48, risedronate resulted in a greater reduction from baseline in serum OC than did alfacalcidol at weeks 12 and 24.

No clear differences in serum levels of ALP, Ca, P, and 1,25 $(OH)_2D$ were observed between the groups.

DISCUSSION

Because of their anti-inflammatory and immunosuppressive action, glucocorticoids are used to treat a variety of diseases. In particular, these drugs are indispensable in the treatment of chronic rheumatoid arthritis. However, glucocorticoids also can cause a number of dangerous adverse reactions, one of which is osteoporosis. Enormous progress has been made in the diagnosis and treatment of these adverse reactions. Despite the existence of a number of medications useful in treating glucocorticoid-induced osteoporosis and knowledge of the diagnostic value of BMD and various biochemical markers of bone turnover, there have been few studies that used BMD and bone turnover markers to compare different osteoporosis treatments in Japanese patients with rheumatoid arthritis and glucocorticoid-induced osteoporosis. In the present study, we used change in BMD, urinary NTX, urinary DPD, serum OC, serum BAP, serum ALP, serum Ca, serum P, and serum 1,25 $(OH)_2D$ to compare risedronate and alfacalcidol treatment in such patients.

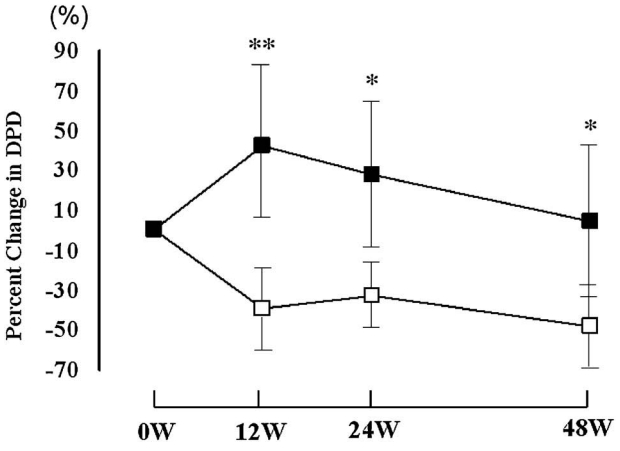

Fig. 3. The Change from Baseline in the Urine DPD for Risedronate (□) and Alfacalcidol (■) Administration after 48 Weeks in Japanese Osteoporosis Patients

Each point represents the mean±S.E. ($n=6$). *=p value of RIS vs. VD_3 (*$p<0.01$, **$p<0.001$).

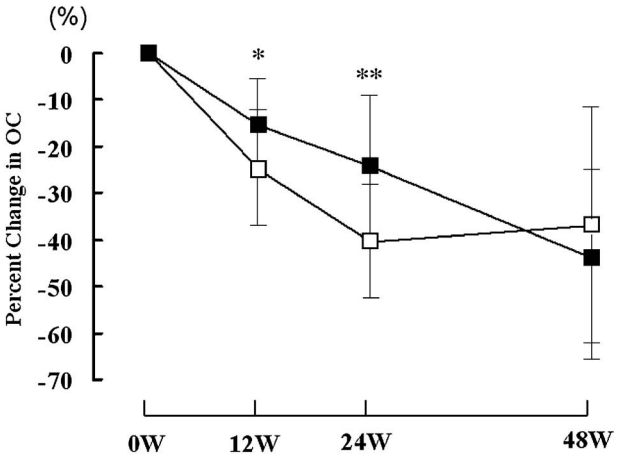

Fig. 4. The Change from Baseline in the Serum OC for Risedronate (□) and Alfacalcidol (■) Administration after 48 Weeks in Japanese Osteoporosis Patients

Each point represents the mean±S.E. ($n=6$). *=p value of RIS vs. VD_3 (*$p<0.05$, **$p<0.01$).

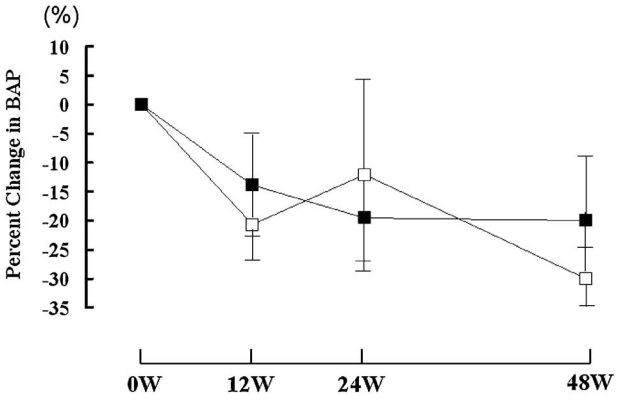

Fig. 5. The Change from Baseline in the Serum BAP for Risedronate (□) and Alfacalcidol (■) Administration after 48 Weeks in Japanese Osteoporosis Patients

Each point represents the mean±S.E. ($n=6$). No significant difference was observed between risedronate and alfacalcidol.

Glucocorticoid-induced osteoporosis is thought to have four main causes. The first cause is thought to be the direct action of glucocorticoid on bone. The collagen and DNA synthesis control, and the decrease in production of osteocalcin and transforming growth factor β (TGF-β), are considered to be direct effects of glucocorticoid on osteoblasts.[15–17] On the other hand, it is also said that it promotes bone absorption revitalization as an action on osteoclasts, though glucocorticoid controls the differentiation of mature osteoclasts. Second, glucocorticoids are thought to act on the enteric canal. They have a direct effect on calcium absorption in the digestive tract.[18] Third, glucocorticoids are thought to act on the kidneys. This depends on a system that increases the amount of calcium filtration because of the increase of the system and the amount of renal blood flow in which glucocorticoid acts directly on renal tubules, and calcium re-absorption is controlled.[19] Fourth, glucocorticoids are thought to act on secretion of endocrine hormones. By their effect on the secretion of pituitary gonadotrophins, glucocorticoids cause decreased secretion of estradiol, testosterone, and dehydroepiandrosterone, and increased absorption of bone.

For the above reasons, we decided to use active VD_3 and bisphosphonate as the medications to treat osteoporosis in the present study. Active VD_3 can be expected to improve a negative calcium balance, act directly on parathyroid cells, and activate osteoblast function. Furthermore, active VD_3 is the most frequently used osteoporosis medication in Japan. Bisphosphonate shows high compatibility with calcium phosphate, and adsorbs to bone without being metabolized in the body. Details of the bone absorption control action are not clear; however, bisphosphonates are thought to control the bone absorption by its deposition to bone being taken into osteoblast.[20]

A number of studies have addressed the clinical meaning of bone turnover markers. In addition, advances have been made in the measurement of such markers, with the technology reaching the point that such measurements are now useful in assessing treatment effects. Monitoring the effects of treatment improves treatment compliance and thereby helps ensure that patients in whom the treatment is effective do not discontinue it. In histological examination of bone from osteoporosis patients, decreases in number of osteoblasts and in osteogenesis are observed, indicating that, metabolically, absorption of bone exceeds osteogenesis in osteoporosis. Also observed are an increase in osteoclasts and an acceleration of bone absorption. Therefore, decreasing the number of bone absorption markers is thought to be very significant in treating glucocorticoid-induced osteoporosis. In the present study, the bone absorption markers NTX and DPD were decreased more by the bisphosphonate risedronate than by active VD_3. This finding was thought to be significant for glucocorticoid-induced osteoporosis. Decreased bone resorption is thought to lead to increased BMD.

Glucocorticoid-induced bone loss is greater in cancellous bone than in cortical bone.[21] This differential effect is explained by the fact that, compared to cortical bone, cancellous bone has 4 times more surface area, which increases exposure to the glucocorticoid, and bone turnover that is 8 times more active. For this reason, we chose to measure BMD of lumbar vertebrae. Our data showed that the bisphosphonate risedronate was effective in increasing BMD (Fig. 1). This effect was attributed to the potent suppressive action of bisphosphonates on bone absorption. As for alendronate, this bisphosphonate was shown to be effective in protecting the spine from fractures in postmenopausal women with low bone mass.[22] Bisphosphonates have also been found to be effective against glucocorticoid-induced osteoporosis in randomized, placebo-controlled clinical studies.[23,24] Guidelines put out by the UK Consensus Group made bisphosphonates the first choice for treatment of glucocorticoid-induced osteoporosis.[3]

Although the number of patients in this study was very small and therefore the statistical power was limited, treatment by bisphosphonate was thought to be one of the effective methods.

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