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ORIGINAL ARTICLE

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Alendronate in rheumatoid arthritis patients treated with methotrexate and glucocorticoids

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Abstract Rheumatoid arthritis (RA) is a systemic inflammatory disease. Along with synovial joint inflammation, extra-articular involvement is a common feature of RA. Periarticular and generalized osteoporosis are seen both as an extra-articular feature of the disease itself and due to various medications like glucocorticoids and methotrexate (MTX). In this study, we investigated the effects of oral alendronate in RA patients treated with MTX and prednisolone by comparing the effects of "alendronate + calcium" and "only calcium" on bone mineral density (BMD). Fifty RA patients classified according to American Rheumatism Association (ARA) criteria were included in the study. The control group consisted of 20 postmenopausal osteoporotic patients. The RA patients were divided randomly into two groups. All patients were started on MTX 7.5 mg/week, 2.5-mg daily folic acid, and 7.5-mg daily prednisolone. The first group, consisting of 25 female RA patients, was also given 10-mg daily alendronate and 1000-mg daily calcium. The second group also consisted of 25 female patients and was given only 1000-mg calcium per day. The postmenopausal control group was given daily 10-mg alendronate and 1000-mg calcium. Bone mineral densities were measured by dual-energy *x*-ray absorptiometry (DEXA) and again at the end of the sixth month. At the end of the study, RA patients given only calcium had reduced mean BMD, and patients treated with alendronate and calcium showed increased mean BMD almost in all regions. This increase was significant in the L2 and L1–4 total regions. In postmenopausal osteoporotic patients, we saw statistically significant increases in BMD in all regions. The increase in BMD values in RA patients treated with alendronate was smaller than in those of the control group of postmenopausal osteoporosis patients. In conclusion, RA itself has a risk factor for osteoporosis in addition to the risks of the medications like corticosteroids and MTX. In the prevention and treatment of RA-associated osteoporosis, alendronate and calcium therapy is effective and well tolerated.

Key words Rheumatoid arthritis · Osteoporosis · Methotrexate · Alendronate · Treatment

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Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disease characterized by serositis, rheumatoid nodules, and vascular inflammation [1]. Its prevalence in developed countries varies between 0.5% and 1% [2].

Along with synovial joint inflammation, extra-articular involvement is a common feature of RA. This involvement includes rheumatoid nodules, vasculitis, and cardiac, pulmonary, renal, bone (osteoporosis), and gastrointestinal involvement, and must be taken together with neuromuscular, ocular, laryngeal, and ophthalmologic findings [1, 3].

Periarticular and generalized osteoporosis are seen in RA, and the risk of fracture increases [1, 3–5]. While periarticular or localized bone loss is seen in the early phase of the disease, generalized osteoporosis develops later [6]. Periarticular bone loss in RA is related to increased vascularity and direct invasion of pannus and also is related to mediators of the inflammation in the joints [6].

Various medications used in the treatment of RA such as glucocorticoids and methotrexate (MTX) result in both localized and generalized bone loss [6, 7]. In RA, age, sex, body height, parity, duration of menopause, history of alcohol or tobacco use, and dietary habits affect bone mineral density (BMD) [5].

There are some mechanisms for the decrease in bone mineral density in RA: use of corticosteroids results in

increased secretion of inflammatory cytokines (IL-1, IL-6, TNF, mast cell heparin, and prostaglandins), all of which increase bone resorption. Another factor partially affecting decreased bone mass is reduced mobility in RA. In addition, for the postmenopausal RA patients, decreased levels of dihydroepiandosterone, estrone, and testosterone lead to osteoporosis [8].

Bisphosphonates are analogues of the natural compound pyrophosphate, but their possession of a carbon atom instead of an oxygen anion enables various structural variations. The pharmacological effect of bisphosphonates is to inhibit bone resorption [9, 10]. Bisphosphonates bind preferably to the active bone "remodeling" sites (resorption). Their release from these sites requires resorption of bone, and hence the half-life of bisphosphonates is quite long (1–10 years) [11]. In postmenopausal women, alendronate treatment normalizes bone turnover rate and an increase in BMD is seen [12]. Alendronate increases lumbar vertebral, femur trochanteric, and total BMD in postmenopausal women regardless of the previous BMD, age, bone turnover rate, history of previous fractures, body height and weight, other medications, and renal function [13].

Various medications used in the treatment of RA can cause osteoporosis. It is well known that long-term use of glucocorticoids may result in osteoporosis. In addition, many authors indicate that with MTX treatment, which has been widely used in treating RA, there may be bone loss [14,15]. Osteoporosis may be seen in RA patients both because of the disease itself and also of the medications such as glucocorticoids and MTX.

In this study, we investigated the effects of oral alendronate in RA patients by comparing the effect of "alendronate + Ca" and "Ca alone" on bone mineral density.

Materials and methods

Fifty RA patients classified according to ARA criteria were included. The control group consisted of 20 postmenopausal osteoporotic patients.

Detailed histories were taken from all patients regarding age, disease duration, disease activity, and previous medications. Exclusion criteria were: (1) history of anticonvulsant, thiazide diuretic, fluoride, calcitriol, or calcitonin treatment, (2) history or presence of malabsorption, metabolic bone disease, and thyroid disease, and (3) immobilization.

A complete blood count, erythrocyte sedimentation rate (ESR), urinalysis, rheumatoid factor (RF), antistreptolysin-O titer (ASO), C-reactive protein (CRP), immunoglobulins (Ig) G, M, and A, complement components C_3 and C_4, serum calcium (Ca), phosphorus (P), alkaline phosphatase (ALP), aspartate transaminase (AST), alanine transaminase (ALT), gamma glutamyl transaminase (GGT), creatinine, albumin, bilirubin, and hepatitis-B surface antigen (HBs Ag) were obtained from all RA patients. The ESR was determined by the Westergren method, and nephelometry was used for the determination of ASO, CRP, RF, Ig G, Ig M, Ig A, C_3, and C_4. Serum biochemical analyses were performed using automated laboratory methods (autoanalyzer). Antinuclear antibody determination was done with immunofluorescence using the Hep-2 cell line. Radioimmunoassay was used for the anti-ds-DNA analysis. Standard anteroposterior (AP) chest and hand X-rays were taken. Hand radiographs were evaluated for the presence of erosions, osteopenia, and joint space loss.

After initial examination, each patient was seen every week during the first month and, later, monthly examinations were performed. Possible side effects were investigated by patient questioning and routine serum analysis at each visit.

The patients were divided into two groups randomly. All were started on MTX 7.5 mg/week, 2.5-mg daily folic acid, and 7.5-mg daily prednisolone. The first group, consisting of 25 female RA patients, was also given 10 mg daily alendronate and 1000 mg daily Ca. The second group, also of 25 female patients, was given only 1000 mg Ca per day. Methotrexate was given on the same day of the week as 3×2.5 mg every 12 h. Folic acid was given on the other days of the week. All patients took prednisolone as a single dose after breakfast. The patients took alendronate in the morning as the first drug with at least a glass of water and were told not to eat anything or take any other drugs and not to lie down during the next half hour. Calcium was used at noontime as 1000-mg effervescent tablets.

Lumbar vertebra AP L1, L2, L3, L4, L1–4 total and right side, femoral neck, trochanteric, intertrochanteric and Ward's regions, and femur total BMD were measured by dual energy X-ray absorptiometry (DEXA) in all the patients, and the measurements were repeated at the end of the sixth month.

A Hologic QDR-2000 X-ray densitometer (Hologic, Waltham, USA) was used in the study. Bone mineral densities were given as grams per square centimeter.

The control group consisted of 20 female postmenopausal patients aged between 50 and 69. They all were diagnosed as osteoporotic after BMD measurements with DEXA, and none had a major medical disease, secondary osteoporosis, or active upper gastrointestinal ulcer. Patients who had been under medication for chronic dyspepsia or medications that could affect bone turnover were excluded. Their AP and lateral lumbar and femoral neck BMD were determined before and 6 months after treatment with 10 mg daily alendronate plus 1000 mg daily Ca. The diagnosis of osteoporosis in postmenopausal patients was made with t-scores below -2.5.

The values before and 6 months after treatment were compared. Student's t-test was used for statistical evaluations and values were considered significant when $P < 0.05$.

Results

Fifty RA and 20 postmenopausal osteoporosis patients were included in the study. They were randomly divided into two groups, each consisting of 25 patients. During follow-up, the following patients were excluded from the study: of the first group, one due to neutropenia and two due to increased liver function; and from the second group, one due to neutropenia, one due to increased liver function, and one due to pulmonary complications. The first group, consisting of 22 patients aged between 35 and 63 years (mean 51.12 ± 9.6), was given MTX, alendronate, and Ca. Disease duration in this group ranged from 6 to 300 months, with a mean of 101.45 ± 97.5 months. The ages of the second group, consisting of 22 RA patients who were given MTX and Ca, were between 22 and 62 years, with a mean of 42 ± 11.6 years. Disease duration in this group ranged between 7 and 360 months, with a mean of 73.18 ± 100.15 months. The age range of the 20 postmenopausal osteoporosis patients was 50–69 years, with a mean of 60 ± 6. In statistical evaluation, there was no significant difference between the ages of the two RA patient

groups ($P > 0.05$), but the ages of postmenopausal osteoporosis patients were significantly higher than those of the RA group ($P < 0.05$).

When we compare the mean levels of Hb, hematocrit, WBC, and platelet counts and ESR, ASO, CRP, RF, Ca, P, and ALP before and 6 months after treatment in the first RA group, which was given MTX plus alendronate plus Ca, no significant differences were seen ($P > 0.05$), except in ESR ($P < 0.05$).

The second group treated with MTX and Ca were also evaluated in the same way. The only significant difference was seen in ESR levels ($P < 0.05$), which decreased with treatment; but the other laboratory parameters showed no statistically significant differences ($P > 0.05$) (Table 1).

In the evaluation of bilateral AP hand radiographs of patients in the MTX plus prednisolone plus alendronate plus calcium and MTX plus prednisolone plus calcium groups before and 6 months after treatment, we did not see development of new erosions, significant changes in osteopenia, or a decrease in joint space.

In the first group of patients, the mean AP L1–4 BMD was 0.959 ± 0.13 g/cm^2 before treatment; after treatment, the mean BMD in the same region was 1.003 ± 0.13 g/cm^2. Mean femur BMD values before treatment were 0.749 ± 0.11 g/cm^2 in the femoral neck, 0.569 ± 0.11 g/cm^2 in the trochanteric region, 0.937 ± 0.17 g/cm^2 in the intertrochanteric area, and 0.615 ± 0.15 g/cm^2 in the Ward's region; and the total score was 0.799 ± 0.13 g/cm^2. After treatment, these values had risen to 0.772 ± 0.10 g/cm^2 in the femoral neck, 0.574 ± 0.11 g/cm^2 in the trochanter, 0.949 ± 0.16 g/cm^2 in the intertrochanteric region, and 0.652 ± 0.12 g/cm^2 in the Ward's region; and the total score was 0.816 ± 0.13 g/cm^2. In the statistical analysis, there were no statistically significant increases seen in AP L1, L3, and L4, femoral neck, trochanteric, intertrochanteric, Ward's region, and femur total mean BMD values ($P > 0.05$); but the differences before and after treatment in L2 and L1–4 BMD measurements were significant ($P < 0.05$).

In the second group of patients, the mean AP L1–4 BMD was 0.900 ± 0.14 g/cm^2 before the treatment; BMD of the same region was 0.908 ± 0.12 g/cm^2 after the treatment. Femur mean BMD values before the treatment were 0.750 ± 0.17 g/cm^2 in the femoral neck; 0.586 ± 0.14 g/cm^2 in the trochanteric region; 0.911 ± 0.24 g/cm^2 in the intertrochanteric area; 0.638 ± 0.21 g/cm^2 in the Ward's region; and the total score was 0.789 ± 0.20 g/cm^2. These values were 0.731 ± 0.17 g/cm^2 in the femoral neck; 0.566 ± 0.14 g/cm^2 in the trochanter; 0.902 ± 0.22 g/cm^2 in the intertrochanteric region; 0.603 ± 0.21 g/cm^2 in the Ward's region; and the total score was 0.767 ± 0.18 g/cm^2 after the treatment. In the statistical analysis there were no statistically significant differences in any of the groups before and after the treatment ($P > 0.05$) (Table 2).

Postmenopausal osteoporosis patients taken as the control group had an age interval of 50 and 69 years (60.04 ± 6.00 years). BMD measurements of these patients were also taken before and after 6 months of treatment with 10 mg daily alendronate and 1000 mg daily Ca. At the beginning of the study, the postmenopausal patient group AP lumbar L1–4 mean BMD value was 0.703 ± 0.11 g/cm^2. After 6 months, L1–4 mean BMD value increased to 0.793 ± 0.10 g/cm^2. Femur mean BMD values before the treatment were 0.595 ± 0.10 g/cm^2 in the femoral neck; 0.503 ± 0.05 g/cm^2 in the trochanteric region; 0.790 ± 0.10 g/cm^2 in the intertrochanteric area; 0.448 ± 0.08 g/cm^2 in the Ward's region; and the total score was 0.664 ± 0.08 g/cm^2. These values were 0.635 ± 0.09 g/cm^2 in the femoral neck; 0.524 ± 0.06 g/cm^2 in the trochanter; 0.814 ± 0.10 g/cm^2 in the intertrochanteric region; 0.488 ± 0.09 g/cm^2 in the Ward's region; and the total score was 0.703 ± 0.08 g/cm^2 after the treatment. In the statistical analysis there were statistically significant differences between pre- and posttreatment mean BMD values in lumbar AP L1, L2, L3, L4, L1–4, femoral neck, intertrochanteric, Ward's regions, and femur total ($P < 0.05$) (Table 3).

Table 1 Laboratory values of first and second groups at the beginning and at sixth months of therapy. (*AP* anteroposterior, *ALP* alkaline phosphatase, *ASO* antistreptolysin-O titer, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *RF* rheumatoid factor)

	Group 1[a]			Group 2[b]		
	Before treatment	At 6 months	Significance	Before treatment	At 6 months	Significance
Hemoglobin (g/dl)	12.05 ± 1.96	12.08 ± 2.10	NS	11.80 ± 1.70	11.99 ± 1.22	NS
Hematocrit (%)	35.86 ± 5.15	36.66 ± 4.78	NS	35.58 ± 4.41	35.88 ± 3.20	NS
WBC count (cells/μl)	6472 ± 1640	7290 ± 1903	NS	7481 ± 1545	7381 ± 1581	NS
Platelet count (cells/μl)	326828 ± 67397	319545 ± 96266	NS	325000 ± 96968	356090 ± 69229	NS
ESR (mm/h)	70.12 ± 25.41	53.74 ± 30.15	$P < 0.05$	59.54 ± 25.78	40.90 ± 29.61	$P < 0.05$
ASO titer (IU/ml)	204.45 ± 14.74	203.36 ± 11.15	NS	242.45 ± 78.64	256.81 ± 109.54	NS
CRP (mg/l)	23.64 ± 16.36	12.09 ± 8.27	NS	22.18 ± 16.74	18.18 ± 16.30	NS
RF (IU/ml)	270.36 ± 94.77	80.63 ± 34.30	NS	82.48 ± 38.22	57.64 ± 17.68	NS
Ca (mmol/l)	2.32 ± 0.12	2.31 ± 0.05	NS	2.38 ± 0.10	2.34 ± 0.11	NS
P (mmol/l)	1.25 ± 0.19	1.07 ± 0.08	NS	1.18 ± 0.18	1.09 ± 0.19	NS
ALP (IU/l)	111.09 ± 23.22	115.27 ± 24.18	NS	107.45 ± 59.84	109.72 ± 57.65	NS

[a] Age 51.2 ± 9.6 years; disease duration 101.45 ± 97.50 months
[b] Age 42.0 ± 11.6 years; disease duration 73.18 ± 100.15 months

Table 2 Mean bone mineral density values before and after the treatment in the first and second group of patients (*AP* anteroposterior)

	Group 1			Group 2		
	Before treatment	At 6 months	Significance	Before treatment	At 6 months	Significance
AP L1	0.882 ± 0.14	0.894 ± 0.13	NS	0.791 ± 0.11	0.795 ± 0.11	NS
AP L2	0.938 ± 0.13	0.978 ± 0.14	$P < 0.05$	0.882 ± 0.14	0.881 ± 0.11	NS
AP L3	1.004 ± 0.15	1.027 ± 0.14	NS	0.949 ± 0.16	0.960 ± 0.14	NS
AP L4	0.990 ± 0.17	1.038 ± 0.15	NS	0.944 ± 0.14	0.958 ± 0.14	NS
AP L1–4	0.956 ± 0.13	1.003 ± 0.13	$P < 0.05$	0.900 ± 0.14	0.908 ± 0.12	NS
Femoral neck	0.749 ± 0.11	0.772 ± 0.10	NS	0.750 ± 0.17	0.731 ± 0.17	NS
Trochanter	0.569 ± 0.11	0.574 ± 0.11	NS	0.586 ± 0.14	0.566 ± 0.14	NS
Intertrochanteric	0.937 ± 0.17	0.949 ± 0.16	NS	0.911 ± 0.24	0.902 ± 0.22	NS
Femur total	0.799 ± 0.13	0.816 ± 0.13	NS	0.789 ± 0.20	0.767 ± 0.18	NS
Ward's	0.615 ± 0.15	0.652 ± 0.12	NS	0.638 ± 0.21	0.603 ± 0.21	NS

Table 3 Mean bone mineral density (g/cm^2) values before and after treatment in the control group ($P < 0.05$ for all values, *AP* anteroposterior)

	Before treatment	At 6 months
AP L1	0.599 ± 0.11	0.642 ± 0.11
AP L2	0.700 ± 0.14	0.732 ± 0.13
AP L3	0.733 ± 0.13	0.960 ± 0.13
AP L4	0.751 ± 0.09	0.793 ± 0.10
AP L1–4	0.703 ± 0.11	0.746 ± 0.11
Femoral neck	0.595 ± 0.10	0.635 ± 0.09
Trochanter	0.503 ± 0.05	0.524 ± 0.06
Intertrochanteric	0.790 ± 0.10	0.814 ± 0.10
Femur total	0.664 ± 0.08	0.703 ± 0.08
Ward's	0.448 ± 0.08	0.488 ± 0.09

Discussion

Rheumatoid arthritis is a chronic disease that has become an important cause of disability and morbidity [3]. Long-term follow-up of RA patients has shown that, in most cases, irreversible cartilage damage starts with disease onset and continues actively in the first year of the disease. Joint destruction is highest in the first 2 years, and the progression rate decreases later [16]. The main change in the management of RA patients during the last 10 years is early and aggressive treatment with disease-modifying antirheumatic drugs (DMARD). Second-line drug therapy is instituted before the erosions are seen radiologically. It is believed that DMARD therapy should be started in patients with synovitis, notwithstanding the use of nonsteroidal anti-inflammatory drugs (NSAID). Early institution of second-line treatment and other strategies have reversed the traditional pyramid [16].

In recent years, MTX has been the most commonly employed second-line drug in RA due to its higher efficacy and relatively sooner onset of action [17]. In previous studies, a decrease in the appearance of new erosions, degree of periarticular osteoporosis, and the degree of joint space narrowing was reported in RA patients who were given MTX [18]. As in previous studies, in our study new erosions were not detected and no increase in size of previous erosions was seen. However, the relatively short follow-up period (6 months) limited our conclusions on this subject.

Osteoporosis has been reported to be one of a number of extra-articular pathologies in RA patients, especially in elderly women. RA is associated with both localized (periarticular) and generalized osteoporosis [19]. Osteoporosis is reported to be influenced by duration and level of disease activity, functional disability, and ESR. As in patients without RA, age, sex, height, weight, parity, time since menopause, smoking history, and some dietary habits may effect BMD [5].

Clinical response to MTX in RA patients starts at 3–6 weeks but becomes apparent after 1–3 months. It is known that high dose MTX therapy is associated with changes in bone metabolism and osteoporosis [20]. Long-term MTX treatment may result in a decrease in bone formation and cause osteopenia [21]. Patients with RA are at greater risk of osteoporosis, and an increase in this risk due to MTX treatment would be an important clinical problem [15]. Low-dose prednisone may be used as a "bridge therapy" in patients started on second-line drug treatment [16,22]. It is well recognized that corticosteroids used in the treatment of RA have an osteopenic effect. However, the relationship between the dose of corticosteroids and the degree of osteoporosis is not clear yet [19]. These are generally used at less than a daily 10-mg dose of prednisone in RA. Corticosteroid-associated bone loss is greater in bones with higher trabecular bone ratio (vertebrae, hip, distal radius, pelvis, and ribs) [23].

For the treatment of RA-induced osteoporosis, hormone replacement therapy (HRT), calcitonin, and fluoride have been used. Although HRT is effective in the prevention of postmenopausal osteoporosis, it is not applicable to men or in premenopausal women with RA. In addition, most female patients may not tolerate the side effects associated with HRT, such as the return of menstrual bleeding and breast pain, or they may have concerns about the risk of breast cancer. Calcitonin, with its effectiveness in treating osteoporosis, has disadvantages with long-term use, including daily parenteral administration, poor tolerability with up to 20% of

patients developing nausea, and development of antibodies. Fluoride is the only orally administered agent that can stimulate bone formation, and an increase has been shown in vertebral BMD in RA patients treated with fluoride. This drug may result in gastrointestinal bleeding or may inhibit mineralization in peripheral bones [24]. Slow-release preparations with a lower incidence of side effects are not available in our country.

Alendronate is a potent bisphosphonate that increases femoral, vertebral, and total body BMD and prevents vertebral, femoral, and forearm fractures by almost 50% in postmenopausal osteoporotic women [13].

In our study, we used alendronate and calcium in a group of RA patients under treatment with MTX plus steroids. In the other group, we used calcium alone. The postmenopausal osteoporotic group without RA was given alendronate and calcium. At the end of 6-month follow-up in RA patients, we saw statistically significant increases in BMD in all regions. Although RA patients given only calcium had decreases in mean BMD, those treated with alendronate and calcium had increased mean BMD in almost all regions by the end of the study. This increase was significant in L2 and L1–4 total regions. The increase in BMD values in RA patients treated with alendronate was lower than the BMD increase in the control group of postmenopausal osteoporosis patients. This indicates that RA itself has a risk factor for osteoporosis in addition to the risks of drugs such as corticosteroids and MTX. The finding of an increase in BMD in RA patients who were given alendronate and calcium, which is statistically significant in some areas, indicated that alendronate and calcium should be considered in both the prophylaxis and treatment of systemic and periarticular osteoporosis, which is an extra-articular finding of RA. However the 6-month duration of this study limits our interpretations for the following period, and further studies are required for this purpose.

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