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ORIGINAL ARTICLE

The limited effects of anti-tumor necrosis factor blockade on bone health in patients with rheumatoid arthritis under the use of glucocorticoid

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Abstract We investigated the effects of biologics for rheumatoid arthritis (RA) patients on bone mineral density (BMD) and bone metabolic markers (BMM), retrospectively, and also clarified the effects of bisphosphonates (alendronate or risedronate 35 mg/week) and glucocorticoids. Participants in this study comprised 219 patients with RA, including 117 patients treated with biologics (infliximab, $n = 90$; etanercept, $n = 27$) and 102 patients with conventional disease-modifying anti-rheumatic drugs (DMARDs) for 1 year. Changes in BMD at the lumbar spine and total hip and BMMs [urinary type I collagen cross-linked N-telopeptide (NTX) and bone-specific alkaline phosphatase] were measured. BMD of the lumbar spine in both groups and total hip BMD in the biologics group were unchanged during treatment with biologics. However, BMD of the total hip was significantly decreased in the DMARDs group (from 0.731 ± 0.135 to 0.706 ± 0.135 g/cm^2). Patients receiving glucocorticoids without bisphosphonates showed significant decrease in BMD of the total hip compared with patients not receiving glucocorticoids or receiving glucocorticoids with bisphosphonates in both biologics and DMARDs groups. Furthermore, BMD of the lumbar spine increased ($p < 0.05$) for patients in the biologics group who received bisphosphonates. NTX was significantly decreased only in the biologics group. Multiple regression analysis showed that BMD and bone metabolic marker levels correlated positively with bisphosphonate and biologics use and negatively with glucocorticoid use. BMD of the total hip was maintained in the patients using biologics without glucocorticoids or with bisphosphonates, but it was not maintained in the DMARDs patients, even without glucocorticoids or with bisphosphonates. Even if biologics have protective effect against bone loss of RA patients, we should consider reducing the dose of glucocorticoids and adding bisphosphonates for the treatment of osteoporosis.

Keywords Rheumatoid arthritis · Biologics · Bone mineral density · Bone metabolic markers · Glucocorticoid

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Introduction

Rheumatoid arthritis (RA) is an autoimmune disease that is characterized by joint inflammation and joint destruction. RA is associated with subchondral bone erosion, cartilage degradation, and systemic bone loss [1, 2]. Osteoporosis is one of the complications in RA [3]. Previous studies have shown that the frequency of osteoporosis is 15–20 % at the hip and spine in patients with RA [4, 5]. Accelerated generalized bone loss often leads to an increased risk of hip [6–8] or vertebral fracture [8–10]. Oral glucocorticoids are known to have deleterious effects on bone [11–13] and are frequently used in the treatment of RA to suppress inflammation.

The mainstay of RA treatment is the application of disease-modifying anti-rheumatic drugs (DMARDs) [14–16]. DMARD treatment helps to suppress inflammatory activity, which is an important risk factor for osteoporosis in RA, and then might decrease susceptibility to osteoporosis. However, bone mineral density (BMD) has been shown to decrease among RA patients receiving treatment with DMARDs alone [17, 18]. In the past decade, there have been significant advances in treating rheumatoid arthritis, especially for patients whose arthritis does not respond to traditional DMARDs. The most important advance has been the development of a group of drugs called biologic response modifiers, or biologics. Therapy with biologics has been expected to prove efficacious in improving not only disease activity but also focal bone erosions in patients with RA [19]. Anti-tumor necrosis factor (TNF)-α antibodies are now commercially available and have been successfully used in halting both joint inflammation and joint destruction in RA patients [20, 21]. Some experimental investigation into the effects of TNF-α on RA-related osteoporosis has been undertaken. In fact, transgenic mice expressing soluble TNF-α receptor to neutralize TNF-α showed protection against estrogen deficiency-related bone loss [22]. Blockade of TNF-α might thus not only serve to block inflammation but also halt the erosive nature of RA and generalized and localized juxta-articular bone loss.

In this study, we compared changes in BMD between RA patients treated with biologics and RA patients treated using conventional DMARDs alone. BMDs of the lumbar spine and total hip and levels of bone metabolic markers [urinary type I collagen cross-linked N-telopeptide (NTX) and bone-specific alkaline phosphatase (BAP)] were measured at baseline and after about 1 year. The effects of bisphosphonates and glucocorticoids on changes in BMD and bone metabolic markers were analyzed and compared.

Materials and methods

Subjects

This study included a total of 219 patients (191 women, 28 men) with RA. All subjects fulfilled the American College of Rheumatology (ACR) criteria (1987) for adult RA [23]. Patients were enrolled from April 1, 2004, to December 31, 2010 at the Osaka City University Hospital and related satellite clinics. The DMARDs group included 102 patients (91 women, 11 men). The biologics group included 117 patients (100 women, 17 men) requiring biologics therapy for treatment of persistent active disease, despite DMARD treatment with methotrexate. Ninety patients in the biologics group received infliximab (3 mg/kg in weeks 0, 2, and 6, and every 8 weeks thereafter. If the effect of infliximab for RA was insufficient, the next dose up was allowed; 27 patients received etanercept (50 mg/week).

Fifty-six patients (26 %) were taking bisphosphonates (alendronate or risedronate, 35 mg/week) and 27 patients (12 %) were taking active vitamin D $1\alpha(OH)D_3$. The proportion of patients on glucocorticoids and mean dose of glucocorticoids used were higher in the biologics group [DMARD group 2.1 ± 2.4 mg/day ($n = 53$), biologics group 3.7 ± 3.1 mg ($n = 82$)], but the proportions of patients using bisphosphonates and vitamin D did not differ between groups.

RA activity was measured using the disease activity score (DAS) composite index, applying a 28-joint score (DAS-28) [24]. This index included the number of swollen and tender joints, patient's global assessment of disease activity, and erythrocyte sedimentation rate (ESR). Levels of C-reactive protein (CRP), matrix metalloproteinase (MMP)-3, and rheumatoid factor (RF) were also determined by standard methods. Functional disability was evaluated using the modified Health Assessment Questionnaire (mHAQ) [25].

BMD and markers of bone metabolism evaluation

At baseline and after about 1 year, BMD (g/cm^2) was measured at the lumbar spine (second to fourth vertebrae, anteroposterior view) and left hip (total hip) by dual-energy X-ray absorptiometry using a QDR 4500 system (Hologic, Waltham, MA, USA). Quality control for the device was performed by daily assessment of a spine phantom. CV (coefficient of variation) with the lumbar spine was approximately 1 %.

At baseline and after 1 year, NTX and BAP were measured at the same time as BMD.

Statistical analysis

Changes were compared between values at entry and after 1 year for BMD, DAS28, BAP, urinary NTX, ESR, CRP, and MMP-3. In each group, data were compared using Student's paired t test for continuous variables, between baseline and after 1 year. Data for both groups were compared using the unpaired Student's t test for continuous variables. Steinblocker stage and class were compared using the Wilcoxon signed-rank test. Absolute changes were measured and presented as variation, defined as the final value minus the initial value. In multivariate analysis, multiple regression analysis was performed for all patients. Statistical tests were considered significant at the level of $p < 0.05$. All p values were two sided. All analyses were performed using SAS version 9.1 software (SAS Institute, Cary, NC, USA).

Table 1 Clinical, biological, and densitometry data at baseline

Parameter	DMARDs group ($n = 102$)	Biologics group ($n = 117$)	p
Age (years)	60.6 ± 9.7	58.0 ± 10.5	NS
Women [n (%)]	91 (89)	100 (85)	NS
Height (cm)	155.0 ± 9.3	155.0 ± 8.0	NS
Body weight (kg)	53.5 ± 8.2	52.6 ± 8.6	NS
BMI (kg/m^2)	22.3 ± 3.0	21.9 ± 3.3	NS
Disease duration (years)	11.3 ± 10.4	11.4 ± 10.6	NS
Steinblocker stage (I/II/III/IV)	18/34/37/13	4/24/58/31	<0.01
Steinblocker class (I/II/III/IV)	50/40/12/0	32/60/23/2	<0.01
ESR (mm)	46.2 ± 25.1	46.6 ± 27.1	NS
CRP (mg/dl)	0.75 ± 1.26	2.01 ± 2.12	<0.01
MMP-3 (ng/ml)	105.9 ± 93.5	239.6 ± 252.3	<0.01
DAS28-ESR	4.01 ± 1.31	5.41 ± 1.32	<0.01
mHAQ	0.49 ± 0.70	0.84 ± 0.64	<0.01
Patients on methotrexate [n (%)]	76 (75)	106 (91)	<0.01
Mean dose of methotrexate (mg/week)	5.6 ± 3.9	6.4 ± 2.8	<0.01
Patients on glucocorticoid [n (%)]	53 (52)	82 (70)	<0.01
Mean dose of glucocorticoid (mg/day)	2.1 ± 2.4	3.7 ± 3.1	<0.01
Patients on bisphosphonate [n (%)]	24 (24)	32 (27)	NS
Patients on vitamin D [n (%)]	16 (16)	11 (9)	NS
Lumbar spine BMD (g/cm^2)	0.856 ± 0.175	0.869 ± 0.157	NS
Total hip BMD (g/cm^2)	0.733 ± 0.134	0.720 ± 0.137	NS
BAP (U/l)	30.9 ± 11.7	27.6 ± 12.8	NS
Urinary NTX (nmol BCE/mmol·Cr)	59.8 ± 27.8	61.2 ± 59.0	NS
Osteoporosis patients [n (%)]	22 (21.6)	18 (15.4)	NS

Values are shown for each parameter at baseline, expressed as mean ± standard deviation or n (%). Data for both groups (DMARDs and biologics groups) were compared using the unpaired Student's t test for continuous variables and the χ^2 test for discrete variables

DMARDs disease-modifying anti-rheumatic drugs, *BMI* body mass index, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *MMP* matrix metalloproteinase, *DAS* disease activity score, *mHAQ* modified health assessment questionnaire, *BMD* bone mineral density, *BAP* bone-specific alkaline phosphatase, *NTX* type I collagen cross-linked N-telopeptide, *NS* not significant

Role of the funding source

The sponsors of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Demographic and clinical characteristics

Demographic and clinical characteristics of the 219 patients included in the study are shown in Table 1. Mean (± standard deviation) age was 59.2 ± 10.2 years. Mean duration of disease was 11.3 ± 10.5 years. Mean DAS28 score was 4.74 ± 1.49. A total of 135 patients (62 %) were on glucocorticoids (mean dose, 3.0 ± 2.9 mg/day).

When the two groups were compared, Steinblocker stage, Steinblocker class, CRP, MMP-3, DAS28 ESR, and mHAQ were significantly higher in the biologics group than in the DMARDs group, but disease duration showed no significant difference between groups. This result shows that severity of RA activity was higher in the biologics group. The proportion of patients with osteoporosis (defined as BMD < 0.7 g/cm^2 at the lumbar spine) was 21.6 % in the DMARDs group and 15.4 % in the biologics group.

Changes in BMD and markers of bone turnover

In the DMARDs group, lumbar spine BMD did not show any significant decrease after final follow-up. However, total hip BMD was decreased from 0.731 ± 0.135 to 0.706 ± 0.135 g/cm^2 ($p < 0.001$) in the DMARDs group. Regarding markers of bone turnover, the DMARDs group showed a significant decrease in BAP but no significant change in NTX level between baseline and final follow-up (Fig. 1).

In the biologics group, lumbar spine and total hip BMD exhibited no change between baseline and final follow-up. BAP was maintained, but NTX level was significantly decreased, from 61.1 ± 58.5 to 48.6 ± 31.0 nmol/mmol CRE ($p < 0.01$) (Fig. 1).

Effect of glucocorticoids and bisphosphonates on BMD

We examined the effects of glucocorticoids and bisphosphonates on BMD and markers of bone turnover. BMD of the total hip in patients receiving glucocorticoids without bisphosphonates showed a significant decrease ($p < 0.01$)

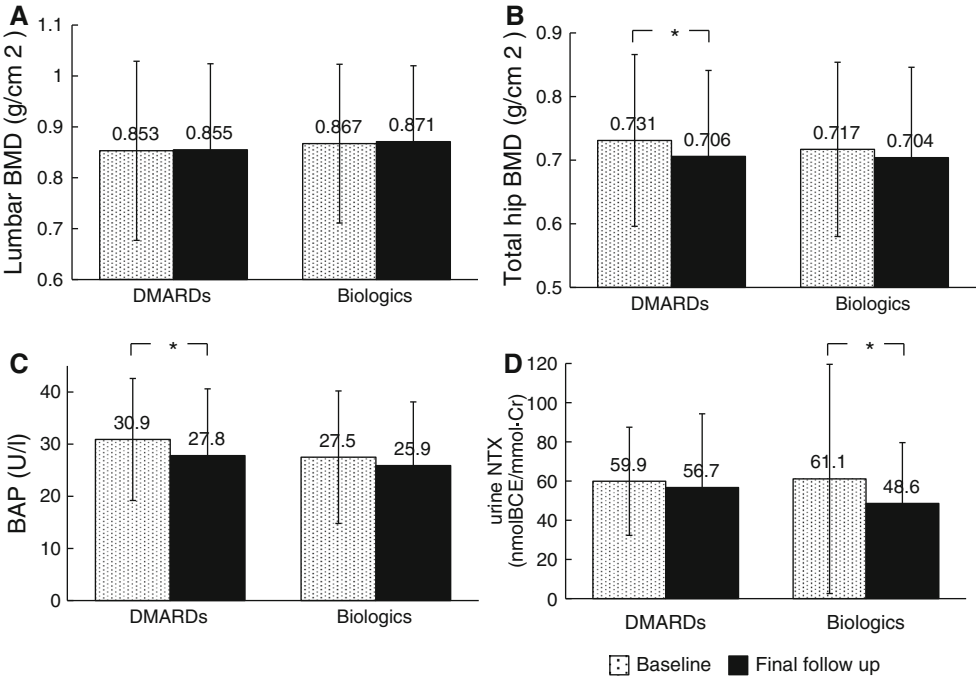

Fig. 1 Changes in bone mineral density (BMD) and bone metabolic markers at baseline and final follow-up: lumbar spine BMD (**a**), total hip BMD (**b**), bone-specific alkaline phosphatase (BAP) (**c**); urinary type I collagen cross-linked N-telopeptide (NTX) (**d**). Values are expressed as mean ± standard deviation. For each parameter, data were compared using Student's paired *t* test for continuous variables, between baseline and final follow-up, $^{*}p < 0.01$. *DMARDs* disease-modifying anti-rheumatic drugs

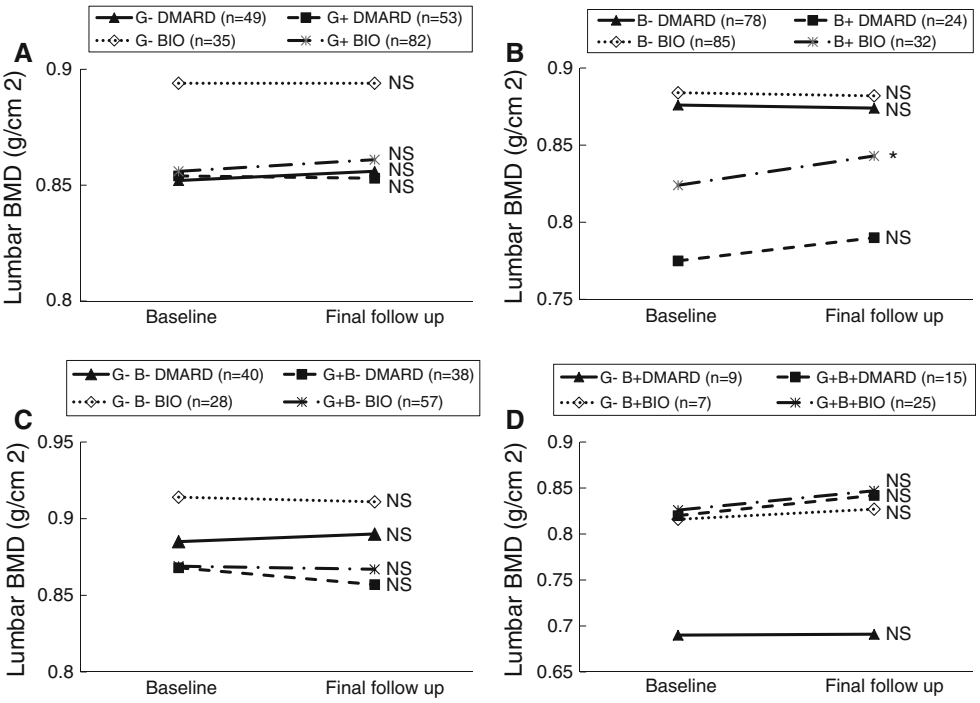

Fig. 2 Effect of glucocorticoids and bisphosphonates on bone mineral density of the lumbar spine. Changes in bone mineral density (BMD) of the lumbar spine at baseline and final follow-up: with or without glucocorticoids (*G*) (**a**), with or without bisphosphonates (*B*) (**b**), with or without glucocorticoids in patients without bisphosphonates (**c**), and with or without glucocorticoids in patients with bisphosphonates (**d**). In each group, data were compared between baseline and final follow-up using Student's paired *t* test for continuous variables. *NS* not significant, $^{*}p < 0.05$

compared with that in patients not receiving glucocorticoids or receiving glucocorticoids with bisphosphonates in both biologics and DMARDs groups (Fig. 2). Moreover, BMD of the lumbar spine was increased ($p < 0.05$) for patients in the biologics group who received bisphosphonates (Fig. 3).

In the biologics group, mean dose of glucocorticoid could be reduced in 32.4 % of patients, from 3.7 ± 3.1 to 2.5 ± 2.7 mg, and 12 patients (14.6 %) were able to cease glucocorticoid use by final follow-up. On the other hand, in the DMARDs group, mean dose could be reduced in 38.1 % of patients, from 2.1 ± 2.4 to 1.3 ± 2.0 mg, and

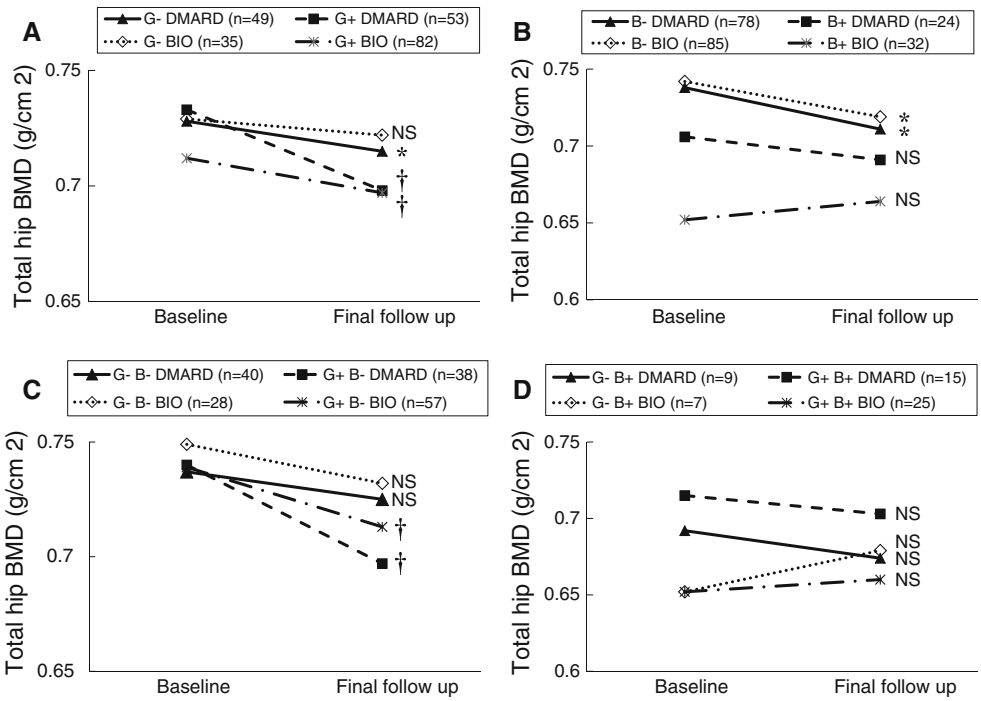

Fig. 3 Effect of glucocorticoids and bisphosphonates on bone mineral density of the total hip. Changes in bone mineral density (BMD) of the total hip at baseline and final follow-up: with or without glucocorticoids (*G*) (**a**), with or without bisphosphonates (*B*) (**b**), with or without glucocorticoids in patients without bisphosphonates (**c**), and with or without glucocorticoids in patients with bisphosphonates (**d**). In each group, data were compared between baseline and final follow-up using Student's paired *t* test for continuous variables. *NS* not significant, $^{*}p < 0.05$, $^{\dagger}p < 0.01$

17 patients (32.0 %) were able to cease glucocorticoid use during the study period.

Multiple regression analysis

Multiple regression analysis was used to examine the specific effects of biologics, bisphosphonates, and glucocorticoid on bone metabolism. Explanatory variables included in the analysis were sex (categorical); age (continuous); body weight (continuous); duration of RA (continuous); baseline ESR (continuous); biologics use (categorical); bisphosphonate use (categorical); glucocorticoid use (categorical); and vitamin D use (categorical). Multiple regression analysis using lumbar BMD as a dependent variable identified bisphosphonate use as a positive independent variable (Table 2A). Biologic use and bisphosphonate use were associated with increased total hip BMD, whereas glucocorticoid use and vitamin D use were associated with decreases in total hip BMD (Table 2B). Bisphosphonate use was associated with decreases in both BAP (Table 2C) and NTX (Table 2D).

Relationship to biologics response

Sixty-six patients receiving biologics were classified as good responders, defined by an improvement ≥1.2 in DAS28 ESR score at final follow-up. The change in lumbar spine BMD was +0.2 % (0.870 ± 0.138 g/cm^2 at baseline; 0.872 ± 0.132 g/cm^2 at final follow-up) for non-responders and −0.2 % (0.883 ± 0.170 g/cm^2 at baseline and 0.882 ± 0.164 g/cm^2 at final follow-up) for responders. The change in BMD at the total hip was +0.6 % (0.746 ± 0.128 g/cm^2 at baseline and 0.751 ± 0.119 g/cm^2 at final follow-up) in non-responders and −2.1 % (0.715 ± 0.142 g/cm^2 at baseline and 0.700 ± 0.142 g/cm^2 at final follow-up) in responders. No significant difference in BMD change was seen between responders and non-responders. Similarly, no significant difference in bone metabolic markers BAP and NTX was apparent between responders and non-responders.

Discussion

Several biologics targeting cytokines, chemokines, and adhesion molecules have been developed for RA therapy. Biologics usually work quickly to relieve the symptoms and swelling associated with RA. Joint destruction is also prevented, and good influences on bone metabolism are expected. The causes of osteoporosis of RA patients are multifactorial and could be associated with the disease itself, or decreased physical activity [26], or treatment with glucocorticoids [27], or also common postmenopausal osteoporosis [26–28]. High BMD loss in RA patients is reportedly associated with joint damage progression, disease activity, functional disability, and immobility, even in early RA [2, 29–32]. However, several observational studies were performed without enrolled control groups. A 1-year case-control study was performed to compare changes in BMD between RA patients treated with infliximab and those not

Table 2 Analysis of the effects of biologics on BMD using multiple regression analysis

Variable	Parameter estimate	Standard error	*t*	Pr > |t|
A: Independent variable; change of lumbar BMD				
Sex	−0.02144	0.01092	−1.96	0.0509
Age	0.00015861	0.00036619	0.43	0.6654
Body weight	−0.00015429	0.00043471	−0.35	0.723
RA duration	−0.00018952	0.00032806	−0.58	0.5641
ESR	−0.00029094	0.0001318	−2.21	0.0284
Biologics use	0.00129	0.00699	0.18	0.8543
Bisphosphonate use	0.01718	0.00848	2.03	0.0441
Glucocorticoid use	−0.00053896	0.00122	−0.44	0.6587
Vitamin D use	−0.01049	0.01072	−0.98	0.3287
Baseline lumbar BMD	−0.07828	0.02277	−3.44	0.0007
B: Independent variable; change of total hip				
Sex	0.00191	0.01232	0.15	0.8772
Age	−0.00108	0.00041175	−2.62	0.0094
Body weight	0.00112	0.00051626	2.17	0.0308
RA duration	0.00022307	0.00038954	0.57	0.5675
ESR	−0.00004203	0.00014855	−0.28	0.7775
Biologics use	0.01728	0.00794	2.18	0.0307
Bisphosphonate use	0.03251	0.00957	3.4	0.0008
Glucocorticoid use	−0.00548	0.00138	−3.96	0.0001
Vitamin D use	−0.03256	0.0123	−2.65	0.0088
Baseline total hip BMD	−0.13479	0.03326	−4.05	<.0001
C: Independent variable; change of BAP				
Sex	4.27187	2.3578	1.81	0.0719
Age	0.10708	0.08064	1.33	0.1861
Body weight	0.11899	0.09962	1.19	0.2341
RA duration	0.05932	0.08215	0.72	0.4713
ESR	0.02508	0.02965	0.85	0.3989
Biologics use	0.82828	1.60442	0.52	0.6064
Bisphosphonate use	−6.30036	1.99782	−3.15	0.0019
Glucocorticoid use	0.35226	0.27889	1.26	0.2084
Vitamin D use	3.59587	2.57418	1.4	0.1644
Baseline BAP	−0.44267	0.06455	−6.86	<.0001
D: Independent variable; change of NTX				
Sex	8.72871	6.54771	1.33	0.1845
Age	0.13142	0.21738	0.6	0.5464
Body weight	−0.1272	0.27265	−0.47	0.6415
RA duration	0.40796	0.2057	1.98	0.0492
ESR	0.06092	0.08322	0.73	0.4653
Biologics use	−7.58094	4.45784	−1.7	0.0911
Bisphosphonate use	−15.04234	5.60764	−2.68	0.0081
Glucocorticoid use	0.26065	0.76822	0.34	0.7349
Vitamin D use	13.23299	7.58125	1.75	0.0829
Baseline NTX	−0.64556	0.04288	−15.06	<.0001

Parameters of the model: $R^2 = 0.0922$, $R^2 = 0.1684$, $R^2 = 0.2426$, $R^2 = 0.5943$. Explanatory variables included in the analysis were sex (categorical), age (continuous), body weight (continuous), disease duration of RA (continuous), ESR (continuous), biologics use (categorical), bisphosphonates use (categorical), glucocorticoid use (categorical), and vitamin D use (categorical)

ESR erythrocyte sedimentation rate, *BMD* bone mineral density, *BAP* bone-specific alkaline phosphatase, *NTX* type I collagen cross-linked N-telopeptide

receiving this agent [33]. In that study, the control group ($n = 99$) showed a significant decrease in BMD (−3.4 % at total hip and −3.9 % at lumbar spine; $p < 0.001$), whereas no decrease was observed in the group treated using methotrexate and infliximab ($n = 90$). In our multiple regression analysis, use of biologics and bisphosphonates was positively correlated with BMD whereas glucocorticoid use was negatively correlated with BMD.

Bone remodeling is the result of two opposing activities: production of new bone matrix by osteoblasts and destruction of existing bone by osteoclasts. Biochemical markers of bone turnover are substances in the blood or urine that are produced or released during bone remodeling. Lange et al. [34] reported persistent increases in OC and decreases in CTX-I among 26 patients with RA treated using infliximab for 1 year. Another report noted that bone resorption was restrained and bone metabolism improved according to measured concentrations of CTX-I and ICTP during treatment with infliximab [35]. In our study, suppression of bone resorption was also confirmed in improvement of urinary NTX. However, in the bisphosphonates group, because bisphosphonates were used before the introduction of biologics, NTX already showed lower levels on the baseline. No change in NTX was therefore recognized.

These findings suggest that biologics can lower NTX levels and may exert positive influences on bone metabolism for the whole body.

Furthermore, the dose of glucocorticoid is a very important factor determining the intensity of influence in bone metabolism. In this study, mean doses of glucocorticoid at baseline were 2.1 ± 2.4 and 3.7 ± 3.1 mg/day in DMARDs and the biologics group, respectively. So, even at the low dose of glucocorticoid, less than 5 mg/day, glucocorticoid has harmful effects on BMD and bone metabolic markers.

Several limitations to the present study must be considered when interpreting the findings. In this study, we included patients with therapy that was not always constant, such as variations in methotrexate and glucocorticoid doses during the investigation period. Furthermore, mean dosages of methotrexate were substantially lower than those seen in Europe and America, because the upper limit for methotrexate in Japan was 8 mg/week until February 2011.

To the best of our knowledge, this represents the first study to examine the effects of biologics, DMARDs, glucocorticoids, and bisphosphonates on BMD in RA patients and to compare the findings with the results for a control group. In this study, BMD loss at the total hip was prevented by the use of biologics and bisphosphonates. However, biologics were unable to prevent BMD loss under glucocorticoid use. Reductions in the dosage of glucocorticoid or administration of bisphosphonates may be necessary to maintain or increase BMD during administration of biologics for RA.

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Conflict of interest Dr. Koike has received research grants and/or speaking fees from Takeda Pharmaceutical, Mitsubishi Tanabe Pharma Corporation, Chugai Pharmaceutical, Eisai, Abbott Japan, Teijin Pharma, Banyu Pharmaceutical, and Ono Pharmaceutical. The other authors have no conflicts of interest to disclose.

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