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Predictors of denosumab efficacy in treating osteoporosis in patients with rheumatoid arthritis: a Japanese multicenter study

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ABSTRACT

We investigated 2-year outcomes of denosumab treatment for osteoporosis in patients with rheumatoid arthritis (RA) and predictors of good outcomes. Study participants were 74 females treated with denosumab for 24 months. After investigating baseline demographics and overall time course for each patient, we divided all cases into two groups according to percent change (%) in bone mineral density (BMD) of lumbar spine (LS-) and total hip (TH-) at 24 months (-24m); two thirds of the patients were allocated to the good outcome group (LS-GO and TH-GO), and the other third to the non-good outcome group (LS-NG and TH-NG). We performed multivariate analysis to confirm predictors of greater increases in LS- and TH-BMD. LS-BMD-24m and TH-BMD-24m increased significantly from baseline. We observed greater %LS-BMD-24m in LS-GO group than in LS-NG group, while %TH-BMD-24m showed no significant group-dependent difference. N-terminal propeptide of type 1 collagen (P1NP) and tartrate-resistant acid phosphatase (TRACP)-5b decreased more in LS-GO group than in LS-NG group at each time point. We observed greater %TH-BMD-24m in TH-GO group than in TH-NG group, while %LS-BMD-24m showed no significant group-dependent difference. Only P1NP-6m showed a larger decrease in TH-GO group relative to TH-NG group. Multivariate analysis confirmed that the larger decrease in P1NP-6m was associated with the greater increase in LS-BMD-24m, while the combined use of biologics was associated with the greater increase in TH-BMD-24m. In conclusions, denosumab increased BMD in RA patients with osteoporosis. The combined use of biologics and denosumab may provide useful treatment options.

Keywords: rheumatoid arthritis, osteoporosis, denosumab, bone mineral density, biologics

Abbreviations and acronyms:
ACPA: anti-citrullinated protein/peptide antibody
BMD: bone mineral density
BMI: body mass index
BP: bisphosphonate
CRP: C-reactive protein
DAS28-CRP: 28-joint disease activity score with CRP
eGFR: estimated glomerular filtration rate
GO: good outcome group

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LS: lumbar spine
mHAQ: modified health assessment questionnaire
MMP-3: matrix metalloproteinase-3
MTX: methotrexate
NG: non-good outcome group
PSL: prednisolone
P1NP: N-terminal propeptide of type 1 collagen
RA: rheumatoid arthritis
RAOP: osteoporosis in RA patients
RF: rheumatoid factor
TH: total hip
TPTD: daily teriparatide
TRACP-5b: tartrate-resistant acid phosphatase-5b

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic disease characterized by persistent synovitis, systemic inflammation, and joint destruction.[1] Early intensive treatment using methotrexate (MTX), biologics, and Janus kinase inhibitor is recommended by the European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR),[2,3] and has led to better outcomes in RA patients.

Although medications for RA have improved, osteoporosis is still recognized as a major complication of RA.[4] Ochi et al[5] reported no decrease in incidence of non-vertebral fracture, despite improvements in RA disease activity during a 10-year period in a Japanese cohort study. Osteoporosis and osteoporosis-related fractures occur more frequently in RA patients than in healthy individuals due to risk factors such as high disease activity, immobility, and the use of glucocorticoids such as prednisolone (PSL).[6,7] Osteoporosis-related fractures often lead to pain, disability, and reduced quality and quantity of life.[8] As past history of vertebral or non-vertebral fragility fractures is a risk factor of future fragility fractures and aggravates life prognosis,[9-11] we believe that treatment of osteoporosis in RA patients (RAOP) is important.

The receptor activator of nuclear factor-kappaB ligand (RANKL) expression of osteoblasts and osteocytes induces osteoclastogenesis, bone resorption, and osteoporosis.[12-14] Some have reported on the association between proinflammatory cytokines and osteoclastogenesis.[15-17] While TNF-α causes osteoclastogenesis with permissive levels of RANKL,[15] IL-6/sIL-6R complex directly induces RANKL expression in synovial fibroblasts in RA,[16] and RANKL expression and osteoclastogenesis are associated with activated Th17 cells in RA.[17] Denosumab, a fully human monoclonal antibody to RANKL, blocks binding of RANKL to RANK, inhibits the development and activity of osteoclasts, decreases bone resorption, and increases bone mineral density (BMD).[18]

Although the efficacy of denosumab on postmenopausal soteoporosis and on joint destruction in RA patients has been reported by several clinical trials,[18-20] reports of the efficacy of denosumab on RAOP are lacking. The present study aimed to evaluate 2-year outcomes of denosumab treatment for RAOP and confirm predictors of greater increases in BMD in clinical settings.

MATERIALS AND METHODS

Patients

The Tsurumai Biologics Communication Registry for osteoporosis (the TBCR-BONE) was

developed in 2013 to explore long-term prognoses for treatment with new agents among patients with primary osteoporosis, glucocorticoid-induced osteoporosis, and RAOP in clinical practice. This registry comprised data from patients who were undergoing denosumab treatment, all of which were serial cases within the medical insurance system in Japan. For the present study, we recruited 87 RA patients who started denosumab treatment between October 2013 and April 2015 and who were registered with the TBCR-BONE. We excluded 4 patients because they were males. Of the remaining 83 RAOP females, 9 were excluded due to the discontinuation of denosumab treatment within 24 months. Ultimately, data from 74 of the original 87 (89.2%) RAOP females who completed 24 months of denosumab treatment at Nagoya University Hospital, Toyohashi Municipal Hospital, or Toyota Kosei Hospital, were used for the analysis in this retrospective cohort study. All patients met the 1987 ACR classification criteria for RA[21] or the 2010 ACR-EULAR classification criteria for RA[22] and fulfilled the definition of osteoporosis in the Japanese 2011 guidelines for prevention and treatment of osteoporosis[23] or the 2004 guidelines on the management of glucocorticoid-induced osteoporosis of the Japanese Society for Bone and Mineral Research.[24] All patients received denosumab 60 mg infusions every 6 months according to the drug label. Patient anonymity was maintained during data collection, and the security of personal information was strictly controlled. This study was approved by the Ethics Committee of Nagoya University Hospital (2017-0415), Toyohashi Municipal Hospital (360) and Toyota Kosei Hospital (2017-ST37).

Data Collection and Study Protocol

This retrospective cohort study used the data recorded to the TBCR-BONE. The following demographics were investigated at the initiation of treatment (baseline, 0 months): age, disease duration, body mass index (BMI), joint damage (Steinbrocker stage), daily dysfunction (Steinbrocker class), rheumatoid factor (RF), anti-citrullinated protein/peptide antibody (ACPA), estimated glomerular filtration rate (eGFR), concomitant treatment for RA (MTX, PSL, and biologics), prior treatment for osteoporosis [bisphosphonates (BPs) and daily teriparatide (TPTD)] and past history of fragility fractures. Levels of serum C-reactive protein (CRP) and serum matrix metalloproteinase-3 (MMP-3), 28-joint disease activity score with CRP (DAS28-CRP), and modified health assessment questionnaire (mHAQ) were investigated at baseline, 6, 12, 18, and 24 months as disease parameters and activity of RA. Levels of serum N-terminal propeptide of type 1 collagen (P1NP) and serum tartrate-resistant acid phosphatase (TRACP)-5b were investigated at baseline, 6, 12, 18, and 24 months as bone turnover markers. BMD in the lumbar spine (LS) and total hip (TH) were investigated to evaluate treatment for osteoporosis at baseline, 6, 12, 18, and 24 months. BMD was measured by dual-energy X-ray absorptiometry (DXA, Lunar Prodigy Advance®; GE Lunar).

Statistical Analysis

First, we evaluated overall baseline demographics, time courses of percent change (%) in LS- and TH-BMD, %P1NP, and %TRACP-5b. Baseline demographics were reported using descriptive statistics. All results are expressed as mean ± standard deviation (SD) or a percentage in each table. Data at each time point were compared using Wilcoxon signed-rank test. Following this, we divided all cases into the two groups of %LS- and %TH-BMD, each at 24 months. We defined the two thirds of patients with good outcomes in %LS- and %TH-BMD at 24 months as the LS-GO and TH-GO groups, respectively, and the one third with non-good outcomes in %LS- and %TH-BMD at 24 months as the LS-NG and TH-NG groups, respectively. Baseline demographics, %LS-BMD, %TH-BMD, %P1NP, and %TRACP-5b at 6, 12, 18, and 24 months were compared between the LS-GO and LS-NG groups, and between the TH-GO and TH-NG

groups. To identify predictors of greater increases in LS- and TH-BMD, we performed univariate and multivariate logistic regression analyses. Univariate logistic regression analysis was performed using Mann-Whitney U test for the comparisons of two groups, while Fisher's exact test was used for comparisons of two categorical variables. We defined baseline P1NP and TRACP-5b, P1NP and TRACP-5b at 6 months, and %P1NP and %TRACP-5b at 6 months as potential early-stage indicators of denosumab treatment, in order to investigate the effect of bone turnover markers with regard to increases in BMD. Receiver operating characteristic (ROC) curves were created for these potential early-stage indicators of bone turnover markers, and we defined the strongest indicator of bone turnover marker for the multivariate logistic regression analysis, according to the greatest area under the curve (AUC) of the ROC curve. Multivariate logistic regression analysis was performed for the selected factors with p-values <0.15 in the univariate logistic regression analysis and for the ROC curve data for the selected bone turnover marker. Finally, we investigated reasons for discontinuation and adverse events, including fragility fractures, hyper/hypocalcemia, infection, cancer, osteonecrosis of the jaw, atypical fracture, cardiovascular event, death, and other events.

Statistical significance was defined as $p<0.05$. All analyses were performed with BellCurve for Excel version 2.13. Any cases with missing data were excluded from the analysis.

RESULTS

Baseline demographics

Baseline demographics are shown in Table 1. Mean (±SD) age was 70.2±7.6 years old and RA disease duration was 17.1±12.8 years. Fifty-five patients (74.4%) were categorized into the advanced Steinbrocker stages (III and IV) and 35 patients (47.3%) were categorized into the advanced Steinbrocker classes (III and IV). Mean (±SD) DAS28-CRP score was 2.77±1.20, and mHAQ was 0.90±0.84. Forty-eight patients (64.9%) were treated with MTX, 17 patients (23.0%) with biologics, and 26 patients (35.1%) with PSL, while 24 (32.4%) and 11 (14.9%) patients underwent prior treatment of BPs and TPTD, respectively. Sixty-four patients received supplements of calcium and vitamin D (Denotas® chewable combination tablet, Daiichi Sankyo Co., Ltd.) and 9 patients received eldecalcitol (Edirol® capsule, Chugai Pharmaceutical Co., Ltd.). Mean (±SD) LS-BMD and TH-BMD were 0.818±0.165 g/cm^2 and 0.591±0.090 g/cm^2, respectively. Mean (±SD) P1NP and TRACP-5b were 55.6±33.6 μg/L and 481.6±209.3 mU/dL, respectively.

Overall clinical efficacy of denosumab treatment

Time course data for %LS-BMD, %TH-BMD, %P1NP, and %TRACP-5b are shown in Figure 1. Both %LS- and %TH-BMD showed significant time-dependent increases at 6, 12, 18, and 24 months from baseline. Both %P1NP and %TRACP-5b showed significant decreases over time, at 6, 12, 18, and 24 months from baseline.

Predictors of greater increases in LS-BMD at 24 months

After excluding 3 patients due to missing data for LS-BMD, the remaining 71 patients were divided into the LS-GO (n=47) and LS-NG (n=24) groups, according to %LS-BMD at 24 months. The cut-off was %LS-BMD of 4.0% at 24 months. Baseline demographics are shown in Table 1. Age, rate of MTX use and baseline P1NP differed significantly between the two groups. Figure 2 shows %LS-BMD, %TH-BMD, %P1NP, and %TRACP-5b at 6, 12, 18, 24 months. While %LS-BMD showed a greater increase in the LS-GO group than in the LS-NG group at each

Table 1 Baseline demographics and parameters of bone turnover markers at 6 months

	Overall (n=74)	Divided by percent change in LS-BMD at 24 months (n=71)			Divided by percent change in TH-BMD at 24 months (n=71)		
		LS-GO (n=47)	LS-NG (n=24)	p Value	TH-GO (n=47)	TH-NG (n=24)	p Value
Age (years)	70.2±7.6	71.6±6.6	67.7±9.1	0.062	70.1±7.2	70.9±8.7	0.661
Disease duration (years)	17.1±12.8	15.9±12.1	19.4±14.1	0.358	16.9±12.4	16.7±13.1	0.879
BMI (kg/m^2)	20.0±3.1	20.0±2.8	20.1±3.9	0.734	19.6±3.2	20.9±3.2	0.126
Stage (I / II / III / IV, %)	12.2/13.5/20.3/54.1	12.8/8.5/23.4/55.3	12.5/20.8/16.7/50.0	0.389	14.9/10.6/17.0/57.4	8.3/16.7/29.2/45.8	1.000
Class (I / II / III / IV, %)	5.4/47.3/45.9/1.4	6.4/46.8/44.7/2.1	4.2/45.8/50.0/0.0	0.802	6.4/44.7/46.8/2.1	4.2/54.2/41.7/0.0	0.450
RF (U/mL)	124.5±170.1	103.7±154.0	140.7±165.2	0.516	123.8±184.2	119.6±135.7	0.421
ACPA (U/mL)	317.0±393.5	288.0±370.4	368.4±428.7	0.687	377.1±448.2	202.2±234.8	0.358
eGFR (mL/min/1.73m^2)	71.1±17.1	68.6±17.1	75.0±18.1	0.230	68.5±18.4	74.3±14.9	0.316
MTX use (%)	64.9	57.4	83.3	0.036	63.8	66.7	1.000
PSL use (%)	35.1	36.2	33.3	1.000	33.3	34.0	1.000
PSL dose (mg/day)	3.5±1.2	3.4±1.7	3.4±2.9	0.581	3.2±1.8	4.1±2.8	0.458
Biologics use (%)	23.0	25.5	20.8	0.774	31.9	8.3	0.039
Infliximab (n, %)	1, 1.4	1, 2.1	–	–	1, 2.1	–	–
Etanercept (n, %)	2, 2.7	2, 4.3	–	–	2, 4.3	1, 4.2	–
Adalimumab (n, %)	3, 4.1	1, 2.1	2, 8.3	–	3, 6.4	–	–
Golimumab (n, %)	5, 6.8	3, 6.4	2, 8.3	–	4, 8.5	1, 4.2	–
Tocilizumab (n, %)	1, 1.4	1, 2.1	–	–	1, 2.1	–	–
Abatacept (n, %)	5, 6.8	3, 6.4	1, 4.2	–	5, 10.6	–	–
Prior treatment of BPs (%)	32.4	23.4	45.8	0.110	23.4	45.8	0.063
Prior treatment of TPTD (%)	14.9	17.0	8.3	0.477	10.6	20.8	0.289
CRP (mg/dL)	0.78±1.23	0.80±1.21	0.72±1.33	0.865	0.80±1.32	0.70±1.13	0.932
MMP-3 (ng/mL)	145.1±277.2	161.7±333.8	109.5±128.9	0.468	162.0±337.9	99.5±80.8	0.870
DAS28-CRP	2.77±1.20	2.79±1.22	2.69±1.20	0.696	2.65±1.19	2.71±0.89	0.476
mHAQ	0.90±0.84	0.94±0.90	0.81±0.73	0.833	0.94±0.84	0.79±0.89	0.378

Past history of fragility fracture (%)	41.9	38.3	41.7	0.802	42.6	37.5	0.800
P1NP							
Baseline (μg/L)	55.6±33.6	58.6±30.1	42.4±22.9	0.025	58.9±33.5	48.6±35.5	0.091
6 months (μg/L)	24.8±16.8	22.5±15.4	28.7±18.4	0.137	22.6±14.7	28.4±20.6	0.450
Percent change at 6 months from baseline (%)	–37.6±67.5	–52.6±39.8	–6.5±97.0	0.006	–40.2±77.4	–31.6±49.9	0.038
TRACP-5b							
Baseline (mU/dL)	481.6±209.3	506.3±215.3	403.5±137.1	0.068	506.1±223.6	436.9±185.0	0.224
6 months (mU/dL)	284.3±171.7	259.4±141.8	308.0±182.0	0.358	259.5±136.9	313.6±218.5	0.673
Percent change at 6 months from baseline (%)	–32.7±43.0	–39.6±42.3	–18.6±43.7	0.030	–41.3±34.0	–19.5±55.3	0.203
LS T score	–2.51±1.37	–2.59±1.21	–2.34±1.65	0.770	–2.66±1.38	–2.25±1.40	0.187
TH T score	–2.86±0.75	–2.85±0.75	–2.87±0.76	0.437	–2.91±0.73	–2.79±0.80	0.952

ACPA, anti-citrullinated protein/peptide antibody; BMD, bone mineral density; BMI, body mass index; BP, bisphosphonate; CRP, C-reactive protein; DAS28-CRP, 28-joint disease activity score with CRP; eGFR, estimated glomerular filtration rate; GO, good outcome group; LS, lumbar spine; mHAQ, modified health assessment questionnaire; MMP-3, matrix metalloproteinase-3; MTX, methotrexate; NG, non-good outcome group; PSL, prednisolone; P1NP, N-terminal propeptide of type 1 collagen; RA, rheumatoid arthritis; RF, rheumatoid factor; TH, total hip; TPTD, daily teriparatide; TRACP-5b, tartrate-resistant acid phosphatase-5b.

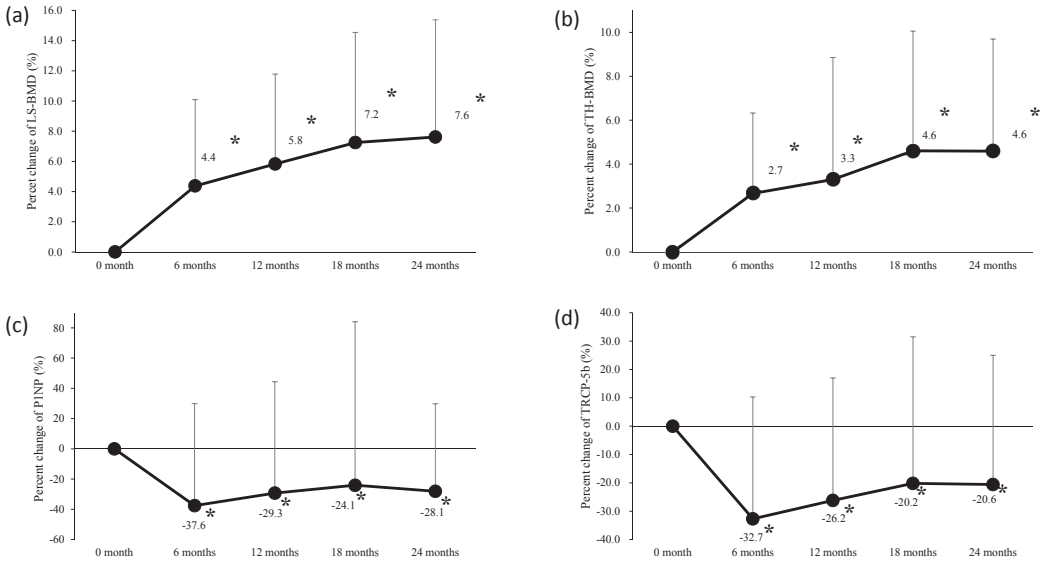

Fig. 1 Overall clinical efficacy of denosumab treatment
Overall time course for percent change of (a) LS-BMD, (b) TH-BMD, (c) P1NP, and (d) TRACP-5b (n=74). *p<0.001 using Wilcoxon signed-rank test from baseline. BMD, bone mineral density; LS, lumbar spine; TH, total hip.

time point, %TH-BMD did not differ significantly between the two groups. Both %P1NP and %TRACP-5b showed greater decreases in the LS-GO group than in the LS-NG group at each time point. According to the AUC of the ROC curve for P1NP and TRACP-5b at baseline, P1NP and TRACP-5b at 6 months, and %P1NP and %TRACP-5b at 6 months, we selected %P1NP at 6 months (p=0.0035) as the strongest early-stage indicator of denosumab treatment (Figure 3). Multivariate logistic regression analysis was performed for demographic factors with p<0.15 and %P1NP at 6 months, and a greater decrease for P1NP at 6 months [Odds ratio (OR) (%) 0.983, 95% confidence interval (CI) 0.968–0.999, p=0.0420] was confirmed as a factor of greater increase in LS-BMD at 24 months (Table 2).

Predictors of greater increases in TH-BMD at 24 months

After excluding 3 patients due to missing TH-BMD data, the remaining 71 patients were divided into the TH-GO (n=47) and TH-NG (n=24) groups according to %TH-BMD at 24 months, with a cut-off of 3.1% at 24 months. Baseline demographics are shown in Table 1. BMI, rate of combined use of biologics and the rate of prior BP treatment differed significantly between these two groups. Figure 4 shows %LS-BMD, %TH-BMD, %P1NP, and %TRACP-5b values at each time point. While %TH-BMD showed a greater increase in the TH-GO group than in the TH-NG group at each time point, %LS-BMD did not differ significantly between the two groups at 24 months. %P1NP at 6 and 24 months, and %TRACP-5b at 18 and 24 months showed greater decreases in the TH-GO group than in the TH-NG group, while %P1NP at 18 months decreased more in the TH-NG group than in the TH-GO group. According to the AUC of the ROC curves for P1NP and TRACP-5b at baseline, P1NP and TRACP-5b at 6 months, and %P1NP and %TRACP-5b at 6 months, we selected %P1NP at 6 months (p=0.0243) as the strongest early-stage indicator of denosumab treatment (Figure 5). Multivariate logistic regression analysis of demographic factors with p<0.15 and %P1NP at 6 months revealed that the combined

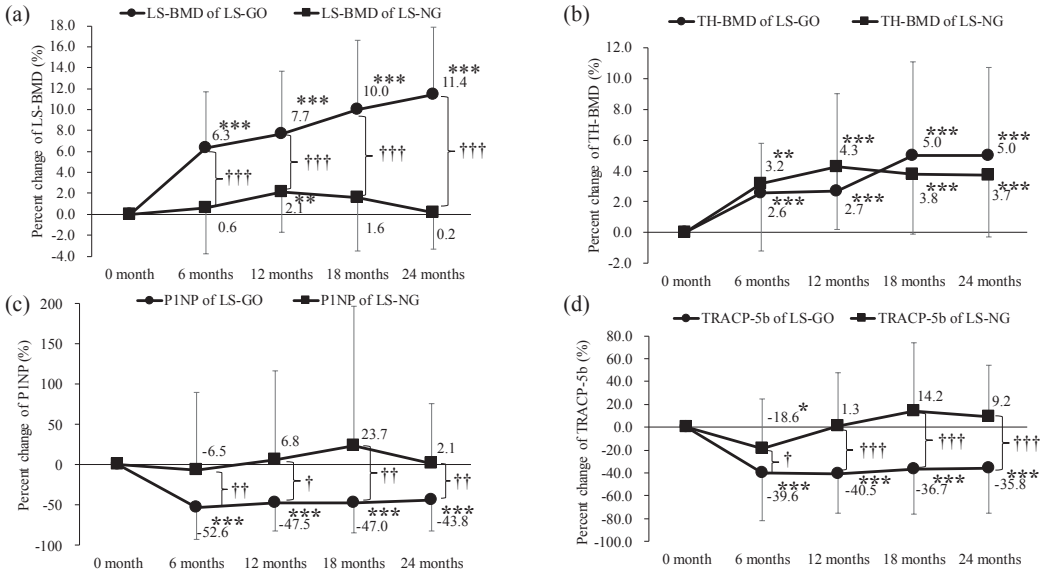

Fig. 2 Time course comparisons between LS-GO and LS-NG

Time course comparisons for percent change of (a) LS-BMD, (b) TH-BMD, (c) P1NP, and (d) TRACP-5b between LS-GO and LS-NG (n=71). *p<0.05, **p<0.01, and ***p<0.001 using Wilcoxon signed-rank test relative to baseline values. †p<0.05, ††p<0.01, and †††p<0.001 using Mann-Whitney U test between groups at each time point. BMD, bone mineral density; GO, good outcome group; LS, lumbar spine; NG, non-good outcome group; P1NP, N-terminal propeptide of type 1 collagen; TH, total hip; TRACP-5b, tartrate-resistant acid phosphatase-5b.

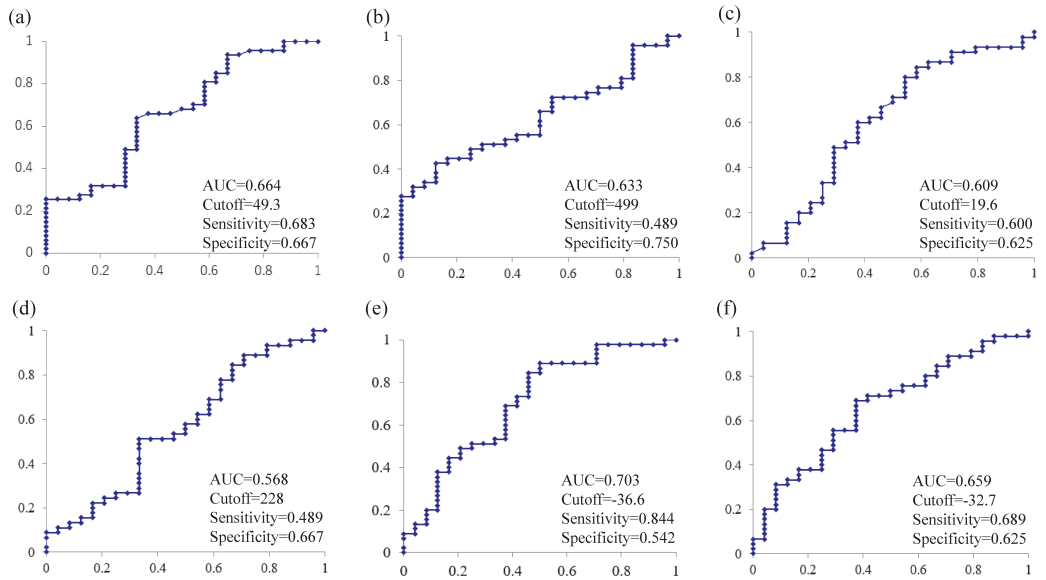

Fig. 3 The AUC of the ROC curve for early-stage indicators of bone turnover markers in LS-GO and LS-NG

The AUC of the ROC curve for (a) P1NP and (b) TRACP-5b at baseline, (c) P1NP and (d) TRACP-5b at 6 months, and (e) %P1NP and (f) %TRACP-5b at 6 months in LS-GO and LS-NG. AUC, area under the curve; GO, good outcome group; LS, lumbar spine; NG, non-good outcome group; P1NP, N-terminal propeptide of type 1 collagen; ROC, Receiver operating characteristic; TRACP-5b, tartrate-resistant acid phosphatase-5b.

Table 2 Univariate and multivariate logistic regression analyses of predictors for greater percent increases in LS-BMD at 24 months

	Univariate		Multivariate		
	Odds ratio	95% confidence interval	Odds ratio	95% confidence interval	p Value
Age (years)	1.074	1.001–1.151	1.094	0.998–1.198	0.0544
MTX use	0.270	0.080–0.914	0.426	0.102–1.773	0.2408
Prior treatment of BPs	0.4052	0.144–1.143	1.027	0.249–4.230	0.9705
Percent change in P1NP at 6 months (%)	0.9859	0.974–0.998	0.983	0.968–0.999	0.0420

BMD, bone mineral density; BP, bisphosphonate; LS, lumbar spine; MTX, methotrexate; P1NP, N-terminal propeptide of type 1 collagen.

Table 3 Univariate and multivariate logistic regression analyses for predictors of greater percent increases in TH-BMD at 24 months.

	Univariate		Multivariate		
	Odds ratio	95% confidence interval	Odds ratio	95% confidence interval	p Value
BMI (kg/m^2)	0.882	0.752–1.035	0.864	0.715–1.045	0.1325
Biologics use	5.156	1.071–24.836	5.812	1.108–30.50	0.0375
Prior treatment of BPs	0.361	0.127–1.031	0.334	0.089–1.251	0.1036
Percent change in P1NP at 6 months (%)	0.998	0.991–1.005	1.003	0.994–1.012	0.5389

BMD, bone mineral density; BMI, body mass index; BP, bisphosphonate; P1NP, N-terminal propeptide of type 1 collagen; TH, total hip.

use of biologics and denosumab (OR 5.812, 95% CI 1.108–30.500, p=0.0375) was confirmed as a factor of greater increase in TH-BMD at 24 months (Table 3).

Adverse events

The 9 cases of discontinuation of denosumab treatment by 24 months included 2 drop-out cases, 3 cases of hospital transfers, 1 case of dysphoria, 1 case of death by lung cancer, 1 case of inadequate response, and 1 case of osteonecrosis of the jaw.

The 74 patients who completed 24 months of denosumab treatment included 1 with asymptomatic hypercalcemia that led to the reduction in supplemental calcium and vitamin D, 1 with asymptomatic hypocalcemia that led to a switch from supplemental calcium and vitamin D to calcium and eldecalcitol, and 2 with leukopenia due to MTX that led to the discontinuation of MTX. Four patients (5.4%) had fractures, including 1 pelvic fracture at 5 months, 1 hip fracture at 13 months, 1 distal femoral fracture at 18 months, and 1 left elbow fracture at 20 months. No adverse events such as infection, new onset of cancer, atypical fracture, or cardiovascular events were noted.

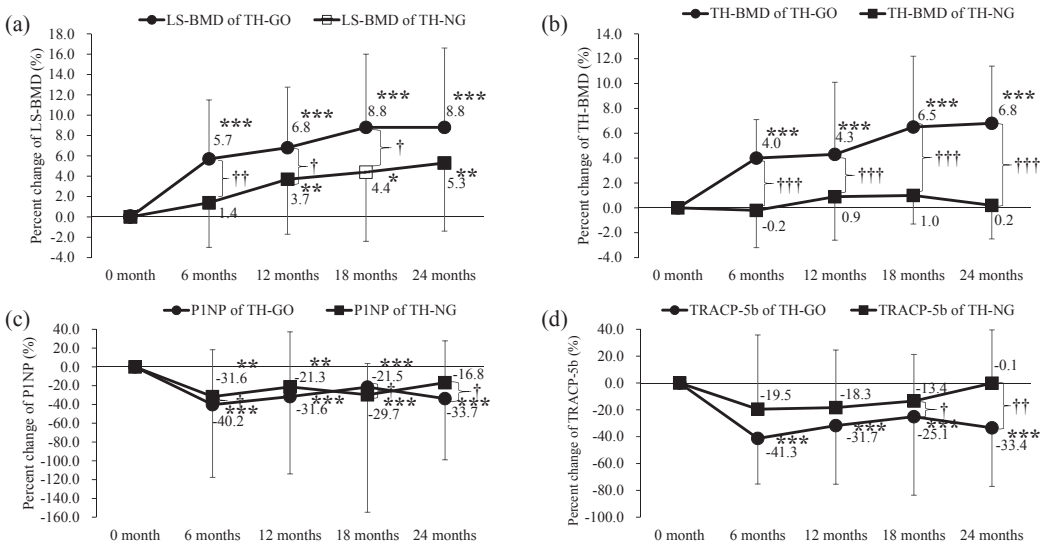

Fig. 4 Time course comparisons between TH-GO and TH-NG

Time course comparisons for percent change of (a) LS-BMD, (b) TH-BMD, (c) P1NP, and (d) TRACP-5b between TH-GO and TH-NG (n=71). *p<0.05, **p<0.01 and ***p<0.001 using Wilcoxon signed-rank test relative to baseline values. †p<0.05, ††p<0.01, and †††p<0.001 using Mann-Whitney U test between groups at each time point. BMD, bone mineral density; GO, good outcome group; LS, lumbar spine; NG, non-good outcome group; P1NP, N-terminal propeptide of type 1 collagen; TH, total hip; TRACP-5b, tartrate-resistant acid phosphatase-5b.

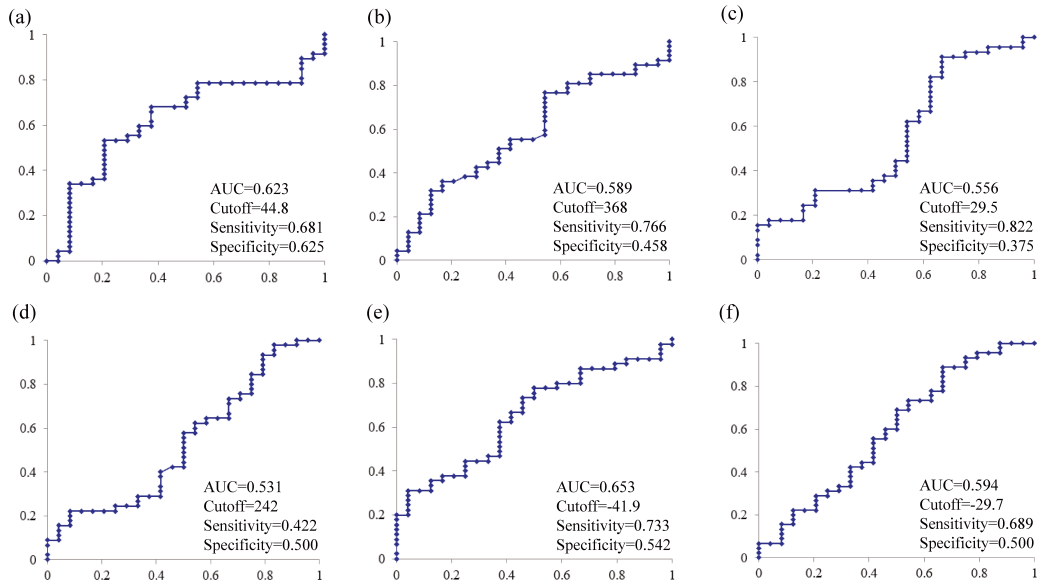

Fig. 5 The AUC of the ROC curve for early-stage indicators of bone turnover markers in TH-GO and TH-NG

The AUC of the ROC curve for (a) P1NP and (b) TRACP-5b at baseline, (c) P1NP and (d) TRACP-5b at 6 months, and (e) %P1NP and (f) %TRACP-5b at 6 months in TH-GO and TH-NG. AUC, area under the curve; GO, good outcome group; NG, non-good outcome group; P1NP, N-terminal propeptide of type 1 collagen; ROC, Receiver operating characteristic; TH, total hip; TRACP-5b, tartrate-resistant acid phosphatase-5b.

DISCUSSION

The present study found that denosumab significantly increased both LS- and TH-BMD in RAOP. In addition, predictors of denosumab treatment efficacy for RAOP differed for LS- and TH-BMD. Univariate analysis showed that non-use of MTX, baseline P1NP, and greater decreases in P1NP and TRACP-5b at 6 months from baseline were significantly associated with a greater increase in LS-BMD at 24 months, and that the combined use of biologics and greater decrease of P1NP at 6 months from baseline were significantly associated with a greater increase in TH-BMD at 24 months. Multivariate logistic regression analysis confirmed that a greater decrease in P1NP at 6 months from baseline was a predictor of a greater increase in LS-BMD at 24 months, and that the combined use of biologics was a predictor for a greater increase in TH-BMD at 24 months.

Previous clinical trials reported that denosumab effectively increased LS- and TH-BMD. Nakamura et al[19] reported that denosumab increased LS- and TH- BMD at 24 months by 9.1% and 4.6% from baseline, respectively, in both postmenopausal women and men with osteoporosis. Takeuchi et al[20] reported that denosumab increased LS- and TH-BMD at 12 months by 4.0–4.7% and 2.4–2.6% from baseline, respectively, compared to that of the placebo in patients with RA, but not osteoporosis. Although direct comparison between our study and these previous studies is difficult because of variability in patient backgrounds, our study findings are consistent with others in that they demonstrate the efficacy of denosumab in increasing LS- and TH-BMD. In addition, our study is one of the few to have reported the efficacy of denosumab treatment for 24 months, specifically among RAOP, and thereby investigated the effect of combined use of biologics and confirmed predictors of greater increases in LS- and TH-BMD. We found that 1) a greater decrease in P1NP at 6 months from baseline was a predictor of a greater increase in LS-BMD at 24 months, but not that in TH-BMD at 24 months, and that 2) the combined use of biologics was a predictor for a greater increase in TH-BMD at 24 months, but not that in LS-BMD at 24 months.

Our study showed that bone turnover markers significantly decreased at each time point from baseline and were maintained at lower levels in the LS-GO group compared to the LS-NG group, and that a greater decrease in P1NP at 6 months was a predictor of a greater increase in LS-BMD at 24 months. It is known that the effectiveness of antiresorptive agents is associated with rapid decrease in bone turnover markers and that rapid decrease in bone turnover by antiresorptive agents is effective to prevent bone loss and to increase in bone mineral density, as bone loss of trabecular bone including lumbar spine is induced by high bone turnover; some reports have found significant associations between short-term decreases in bone turnover markers and the reduced risk of vertebral and nonvertebral fractures with the use of antiresorptive agents.[8,25] While Dore et al[26] reported that baseline P1NP correlated with BMD increases over the course of denosumab treatment, particularly for the LS, we focused on short-term decreases in bone turnover markers during treatment with denosumab. We found that %P1NP at 6 months was more strongly associated with %LS-BMD at 24 months than baseline P1NP. %P1NP at 6 months showed significant decreases from baseline in the LS-GO group, but not in the LS-NG group of the present study. Taken together, this suggests that in the short-term, greater decreases in P1NP could predict a greater increase in LS-BMD during denosumab treatment.

In contrast to LS-BMD, although univariate analysis showed that %P1NP at 6 months was associated with %LS-BMD at 24 months, multivariate logistic regression analysis did not confirm that a greater decrease in P1NP at 6 months was a predictor for a greater increase in TH-BMD at 24 months in our study. Mochizuki et al[27] recently reported that a decrease in P1NP at 3 months, but not at 6 months, from baseline was associated with an increase in TH-BMD at

12 months. Although direct comparison between our study and this previous study is difficult because of variability in patient background, and because of differences in endpoints and statistical methods, these studies consistently found no association between decreases in P1NP at 6 months and increase in TH-BMD.

Our investigation revealed that combined use of biologics and denosumab was a predictor for a greater increase in TH-BMD. Some studies have reported the efficacy of denosumab treatment on both osteoporosis and bone erosion. Cohen et al[27] reported that 12-month denosumab treatment inhibited structural damage, improved BMD, and suppressed bone turnover in RA patients. Takeuchi et al[20] reported that denosumab inhibited the progression of bone erosion and increased BMD. Mochizuki et al[28] reported that denosumab increased the BMD in the LS, TH, femoral neck, and hand, as well as suppressed joint destruction in Japanese patients with RA. Deodhar et al[29] reported that denosumab protected against erosion and increased hand BMD, with a negative correlation between hand BMD and erosion scores. A recent study has also reported that concurrent use of biologics and denosumab in RA patients more effectively inhibited structural damage than treatment with biologics alone.[30] Although no others have studied the efficacy of the combined use of biologics and denosumab on RAOP, our study might newly demonstrate that the combined use of biologics and denosumab was effective not only in treating bone erosion but also in treating RAOP. In this study, the combined use of biologics and denosumab was not effective in inducing a greater increase in LS-BMD, for reasons that remain unclear. Chronic inflammation, mediated by proinflammatory cytokines such as TNF-α and IL-6, is thought to increase the risk of osteoporosis and fracture in patients with RA.[31] Indeed, Lodder et al[32] and Haugeberg et al[33] reported that high disease activity was associated with low BMD in the femoral neck and TH, but not in the LS. Biologics inhibits proinflammatory cytokines, which induce both high disease activity and RANKL expression and osteoclastogenesis in patients with RA. Recent studies have shown that denosumab inhibits bone loss in the joints of patients with RA[20,27-29] and reduces cortical porosity of the proximal femoral shaft in those with osteoporosis[34] Taken together, this suggests that the combined use of biologics and denosumab might strongly inhibit excessive production of cytokines such as TNF-α, IL-6, and RANKL, and improve bone loss in joints such as the hip in patients with RAOP.

MTX osteopathy was initially reported in children with acute leukemia treated with high-dose MTX.[35] However, conflicting findings have been reported on the effect of low-dose MTX in patients with rheumatic disease. While several case series reported stress fractures in patients with rheumatic disease treated with low-dose MTX,[36-38] one large multicenter, cross-sectional study, one prospective study, and one population-based cohort study found no association between low-dose MTX use and change in BMD in RA patients.[39-41] In our study, although univariate analysis identified a negative relationship between MTX use and increase in LS-BMD, multivariate logistic regression analysis confirmed that MTX use was not associated with increases in either LS- or TH-BMD.

Although some have reported that high disease activity and peripheral bone erosion are associated with low BMD,[29,32,33] we found no association between disease activity and increase in BMD. This could be due to lower disease activity in our patients with RA, relative to those in previous studies. In contrast to previous studies, which reported high baseline disease activity levels (mean DAS of 3.2±1.4[32]; and mean DAS28 of 6.6±1.8[33]) in RA, mean DAS28-CRP score for our study population was 2.8±1.2.

The present study had several limitations. First, this was a retrospective cohort study, and the sample size was small, so our data comparisons could have been biased. A prospective study of a larger study population could help verify our results. Second, there was no good evidence for the cut-off of ‘good outcome group’ in this study (4.0% of %LS-BMD and 3.1%

of %TH-BMD at 24 months). Some have noted the importance of identifying treatment targets for osteoporosis[42,43]; most recently, Cummings et al[44] reported that these include starting treatment for a T-score ≤–2.5 at the femoral neck, total hip, or lumbar spine by DXA and a treatment goal of achieving a T-score >–2.5 at those skeletal sites within 3–5 years. However, there are still no clear short-term targets such as yearly percent increases in BMD. Although the cut-off for the present study seemed to be reasonable when time course data for mean %BMD were compared between groups, further studies with certain treatment targets are needed. Third, we could not show clear reasons why factors of greater increases in BMD in lumbar spine and total hip was different. It is known that bone turnover of cortical bone is much slower than that of trabecular bone, which might suggest 1) that even if bone turnover markers decrease and BMD of trabecular bone such as lumbar spine increases, to increase bone mineral density of cortical bone such as total hip might be still difficult, and 2) that if bone mineral density of cortical bone increases, that of trabecular bone could also increase.

In conclusion, denosumab was effective in inducing greater increases in LS- and TH-BMD in patients with RAOP. A greater decrease in P1NP at 6 months was associated with a greater increase in LS-BMD, and combined use of biologics and denosumab was associated with a greater increase in TH-BMD. Further studies of the efficacy of combined use of biologics and denosumab among patients with RAOP are necessary.

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CONFLICT OF INTEREST

Y. Hirano received lecture fees from AbbVie Inc., Eisai Co., Mitsubishi Tanabe Pharma Co., Pfizer Inc., Chugai Pharmaceutical Co., and Bristol-Myers Squibb Co. N. Takahashi received lecture fees from AbbVie Inc., Eisai Co., UCB Japan Co., Mitsubishi Tanabe Pharma Co., Takeda Pharmaceutical Co., Pfizer Inc., Chugai Pharmaceutical Co., Janssen Pharmaceuticals, and Bristol-Myers Squibb Co. N. Ishiguro received grants and lecture fees from Daiichi Sankyo Co., Takeda Pharmaceutical Co., Hisamitsu Pharmaceutical Co., Otsuka Pharmaceutical Co., Taisho Toyama Pharmaceutical Co., Kaken Pharmaceutical Co., Eisai Co., Janssen Pharmaceuticals, Bristol-Myers Squibb Co., AbbVie Inc., Chugai Pharmaceutical Co., Mitsubishi Tanabe Pharma Co., Astellas Pharma Inc., and Pfizer Inc. T. Kojima received lecture fees from Mitsubishi Tanabe Pharma Co., Takeda Pharmaceutical Co., Eisai Co., AbbVie Inc., Bristol-Myers Squibb Co., Pfizer Inc., Janssen Pharmaceuticals, Astellas Pharma Inc., and Chugai Pharmaceutical Co. The other authors declare no conflicts of interest.

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