Conventional synthetic disease-modifying anti-rheumatic drugs and bone mineral density in rheumatoid arthritis patients with osteoporosis: possible beneficial effect of leflunomide

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Abstract

Objective

To investigate the effect of conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) on bone mineral density (BMD) in rheumatoid arthritis (RA) patients with osteoporosis.

Methods

Patients with RA who were newly diagnosed with osteoporosis (T-score ≤ –2.5) between 2010 and 2017 were included. All patients received background bisphosphonate for treatment of osteoporosis. BMD was measured at baseline and after one year. To identify csDMARDs or other factors associated with significant increase in BMD (≥3%) at lumbar spine and femoral neck at one year, we performed logistic regression analysis. To exclude the possibility of confounding by methotrexate, which was commonly used as a combination therapy with other csDMARDs, we also performed logistic regression analysis in the methotrexate users (subgroup analysis).

Results

In total, 153 RA patients with newly diagnosed osteoporosis were included. Leflunomide was the only csDMARD associated with significant increase in lumbar spine BMD (adjusted odds ratio (OR) 3.000, 95% confidence interval (CI) 1.177–7.645, p=0.021). In regard to femoral neck BMD, no csDMARDs were associated with significant increase in BMD. In the subgroup analysis, use of leflunomide was still associated with significant increase in lumbar spine BMD (adjusted OR 2.653, 95% CI 1.030–6.836, p=0.043), whereas no csDMARDs were associated with significant increase in femoral neck BMD.

Conclusion

Among the csDMARDs, leflunomide can be beneficial in lumbar spine BMD in RA patients with osteoporosis.

Key words

rheumatoid arthritis, osteoporosis, bone mineral density, disease-modifying anti-rheumatic drugs

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Introduction

Rheumatoid arthritis (RA) is an autoimmune disorder characterised by chronic inflammation (1). Population-based studies have established that patients with RA are at higher risk of osteoporosis (2, 3), which is characterised by low bone mineral density (BMD) and microarchitectural deterioration of bone tissue, leading to increased risk of fracture (4). Osteoclasts, the cells that are primarily responsible for bone resorption, are one of the key mediators of osteoporosis (5). In patients with RA, inflammatory cytokines such as tumour necrosis factor-α, interleukin-6 (IL-6), and IL-17 induce the differentiation and activation of osteoclasts (6), which partly contribute to the increased risk of osteoporosis. Conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), such as methotrexate (MTX), hydroxychloroquine (HCQ), sulfasalazine (SSZ), leflunomide (LEF), and tacrolimus (TAC), reduce inflammation and progression of structural damage in RA (1, 7). Interestingly, there are some *in vitro* data showing the inhibitory effect of csDMARDs on osteoclastogenesis (8-11). Considering that osteoclasts are the major mediators of osteoporosis (5), csDMARDs, through inhibiting osteoclastogenesis, may have the potential to prevent generalised bone loss. However, despite the presence of *in vitro* data, clinical data reporting the effect of csDMARDs on BMD, particularly in RA patients with osteoporosis, are limited. As patients with RA have higher risk and prevalence of osteoporosis compared to the general population (2, 3), elucidating the effect of csDMARDs on BMD in RA patients with osteoporosis is an important issue to be addressed. Therefore, in this study, we investigated the effect of csDMARDs on BMD in patients with RA who were newly diagnosed with osteoporosis.

Materials and methods

Patients

Patients with RA who were newly diagnosed with osteoporosis at a tertiary referral hospital in Seoul, South Korea between January 2010 and March 2017 were included. All patients met the 2010 American College of Rheumatology/European League against Rheumatism classification criteria for RA (12). For the homogeneity of the study population, the following patients were excluded: patients who received medication other than bisphosphonate for osteoporosis (selective oestrogen receptor modulators, denosumab, and teriparatide), patients not receiving calcium and vitamin D supplementation, patients with underlying thyroid or parathyroid diseases, patients receiving biologic DMARDs or targeted synthetic DMARDs, patients with a history of previous fracture, and current smokers.

The following demographic and clinical data at the time of osteoporosis diagnosis were collected: age, sex, body mass index (BMI), the presence of diabetes mellitus, disease duration of RA, the positivity of rheumatoid factor (RF) and anti-cyclic citrullinated peptide (CCP) antibody. Average value of disease activity score 28 (DAS28)-C reactive protein (CRP) during the study period, and proportion of patients achieving at least low disease activity (DAS28-CRP ≤3.2) at one year were reviewed.

Medications used during the follow-up period were also reviewed. Regarding the use of csDMARDs (MTX, HCQ, SSZ, LEF, and TAC), patients were classified as ever users and never users during the follow-up period of one year from the diagnosis of osteoporosis. Patients who did not achieve low disease activity with MTX monotherapy received usually csDMARDs combination therapy (mostly, MTX based combination with HCQ, SSZ, TAC, or LEF) or other csDMARD monotherapy (SSZ or LEF) depending on physician's preference. As the type and dosage of csDMARDs used in individual patients varied during the follow-up period, the cumulative dose of each csDMARD and length of time each csDMARD was used during the follow-up period were assessed. In addition, data on the usage of glucocorticoids were also collected as a cumulative dose (mg of prednisolone or its equivalent) and length of time it was used during the follow-up period of one year. Type of bisphosphonate used was reviewed as well. This study was approved by the Institutional Review Board of Asan

Medical Center in Seoul, South Korea (IRB No: 2018-0090). Requirement for informed consent was waived because of the retrospective nature of the study.

Outcome definition

BMD was assessed by dual energy x-ray absorptiometry (DXA) scan, which is the gold standard for the non-invasive measurement of BMD (13). Diagnosis of osteoporosis was based on BMD results of lumbar spine T-score ≤-2.5 and/or femoral neck T-score ≤-2.5. In accordance with the American Association of Clinical Endocrinologists and American College of Endocrinology guideline, which recommends BMD testing every 1 to 2 years for patients with disorders that adversely affect bone mass (14), BMD was measured at baseline and after one year at the lumbar spine (first to fourth vertebrae) and femoral neck using DXA scan. All patients included in our study received BMD assessment using the same DXA scan between baseline and after one year.

Previous randomised placebo-controlled trials have shown significant changes in BMD at one year in bisphosphonate receiving patients (15, 16). Based on these data, we assumed that one year of follow-up is sufficient to evaluate significant change in BMD. The percentage change in BMD at one year was assessed. The least significant change in BMD was determined to be 3% at our institute; therefore, BMD increase by ≥3% was considered significant. The proportion of patients achieving significant BMD increase for both lumbar spine and femoral neck at one year was defined as the outcome measure.

Statistical analysis

For description of patient characteristics, continuous variables were expressed as the mean ± standard deviation (SD) or median [interquartile range (IQR)] for normal and non-normal distribution, respectively. Categorical variables were expressed as number (%). For identifying factors associated with the significant increase in BMD at one year, univariable and multivariable logistic regression analyses were conducted. All variables with $p<0.2$ in the univariable analysis were subsequently included in the multivariable analysis. To exclude the possibility of confounding by MTX, which was commonly used as a combination therapy with other csDMARDs, we also performed logistic regression analysis in the MTX users (subgroup analysis). All the analyses were conducted using SPSS v. 20.0.

Table I. Baseline characteristics of the 153 patients with RA newly diagnosed with osteoporosis.

	Total cohort patients (n=153)
Female	141 (92.2%)
Age (years)	64.2 (± 8.6)
RA duration (months) at osteoporosis diagnosis	23.3 (0.0 – 60.2)
RF	114 (74.5%)
Anti-CCP Ab	115 (75.2%)
DM	14 (9.2%)
BMI (kg/m^2)	23.27 (± 3.42)
DAS28-CRP	2.53 (± 0.86)
Patients on at least low disease activity† at 1 year	139 (90.8%)
Cumulative dose of glucocorticoid (mg/year)*	1035.0 (540.0 – 1650.0)
Length of time glucocorticoid was used (days)	266.0 (154.0 – 365.0)
Type of bisphosphonate	
Risedronate	107 (69.9%)
Alendronate	46 (30.1%)
csDMARDs	
Use of MTX	129 (84.3%)
Cumulative dose (mg/year) of MTX	650.0 (520.0 – 780.0)
Length of time MTX was used (days)	365.0 (365.0 – 365.0)
Use of HCQ	81 (52.9%)
Cumulative dose (g/year) of HCQ	73.0 (44.0 – 146.0)
Length of time HCQ was used (days)	365.0 (195.5 – 365.0)
Use of SSZ	42 (27.5%)
Cumulative dose (g/year) of SSZ	362.0 (137.0 – 381.3)
Length of time SSZ was used (days)	295.0 (100.0 – 365.0)
Use of LEF	31 (20.3%)
Cumulative dose (mg/year) of LEF	3540.0 (2740.0–4625.0)
Length of time LEF was used (days)	187.0 (119.0 – 365.0)
Use of TAC	17 (11.1%)
Cumulative dose (mg/year) of TAC	313.0 (177.5 – 557.5)
Length of time TAC was used (days)	176.0 (133.0 – 365.0)
Initial BMD	
Lumbar spine T-score	-2.9 (-3.4 – -2.6)
Femoral neck T-score	-2.2 (-2.8 – -1.6)
1 year % change of	
Lumbar spine BMD	3.60 (1.05 – 7.40)
Femoral neck BMD	1.30 (-1.28 – 3.08)
Significant BMD increment (ΔBMD ≥3%)	
Lumbar spine	87 (56.9%)
Femoral neck	40 (26.1%)

RA: rheumatoid arthritis; RF: rheumatoid factor; anti-CCP Ab: anti-cyclic citrullinated peptide antibody; DM: diabetes mellitus; BMI: body mass index; DAS28-CRP: disease activity score 28-C-reactive protein; csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs; MTX: methotrexate; HCQ: hydroxychloroquine; SSZ: sulfasalazine; LEF: leflunomide; TAC: tacrolimus; BMD: bone mineral density. †DAS28-CRP ≤3.2, *Equivalent to prednisolone.

Results

Patient characteristics

A total of 153 patients with RA who were newly diagnosed with osteoporosis were included. Characteristics of the patients are presented in Table I. The majority (92.2%) of the patients were female with a mean age of 64.2 (±8.6) years. Median disease duration of RA was 23.3 (0.0–60.2) months. RF and anti-CCP antibody were positive in 114 (74.5%) and 115 (75.2%) patients, respectively. Diabetes mellitus was present in 14 (9.2%) patients. Mean values of BMI and DAS28-CRP were 23.27 (±3.42) kg/m^2 and 2.53 (±0.86), respectively. At one year, 139 (90.8%)

Table II. Factors associated with significantly increased lumbar spine BMD at one year.

Univariable analysis

	Unadjusted OR	95% CI	*p*-value
Female	1.400	0.284 – 3.095	0.566
Age	1.346	0.963 – 1.038	0.809
RA duration	0.997	0.991 – 1.002	0.249
RF	1.789	0.859 – 3.723	0.120
Anti-CCP Ab	1.426	0.682 – 2.979	0.346
DM	1.408	0.449 – 4.416	0.558
BMI	0.906	0.821 – 0.999	**0.047**
DAS28-CRP	1.053	0.726 – 1.529	0.784
At least low disease activity† at 1 year	1.356	0.451 – 4.075	0.588
Cumulative dose of glucocorticoid	1.001	0.962 – 1.041	0.972
Type of bisphosphonate (risedronate)	2.177	1.079 – 4.395	0.030
MTX	1.695	0.706 – 4.070	0.238
HCQ	0.646	0.339 – 1.233	0.185
SSZ	0.889	0.435 – 1.817	0.747
LEF	3.211	1.288 – 8.007	**0.012**
TAC	1.447	0.506 – 4.139	0.490

Multivariable analysis

	Adjusted OR	95% CI	*p* value
RF	2.073	0.911 – 4.716	0.082
BMI	0.922	0.831 – 1.024	0.129
Type of bisphosphonate (risedronate)	1.936	0.931 – 4.025	0.077
HCQ	0.536	0.260 – 1.106	0.091
LEF	3.000	1.177 – 7.645	**0.021**

BMD: bone mineral density; OR: odds ratio; CI: confidence interval; RA: rheumatoid arthritis; RF: rheumatoid factor; anti-CCP Ab: anti-cyclic citrullinated peptide antibody; DM: diabetes mellitus; BMI: body mass index; DAS28-CRP: disease activity score 28-C-reactive protein; MTX: methotrexate; HCQ: hydroxychloroquine; SSZ: sulfasalazine; LEF: leflunomide; TAC: tacrolimus.
†DAS28-CRP ≤3.2

Table III. Factors associated with significantly increased femoral neck BMD at one year.

	OR	95% CI	*p*-value
Female	0.571	0.167 – 2.191	0.372
Age	0.382	0.958 – 1.042	0.489
RA duration	0.999	0.993 – 1.006	0.858
RF	1.550	0.644 – 3.732	0.328
Anti-CCP Ab	1.771	0.708 – 4.431	0.222
DM	1.122	0.331 – 3.803	0.853
BMI	1.016	0.914 – 1.130	0.767
DAS28-CRP	0.947	0.622 – 1.442	0.801
At least low disease activity† at 1 year	0.618	0.194 – 1.968	0.415
Cumulative dose of glucocorticoid	0.986	0.941 – 1.033	0.559
Type of bisphosphonate (risedronate)	1.722	0.743 – 3.991	0.205
MTX	1.859	0.591 – 5.841	0.289
HCQ	1.473	0.707 – 3.069	0.301
SSZ	1.212	0.546 – 2.691	0.637
LEF	0.957	0.389 – 2.354	0.905
TAC	0.562	0.153 – 2.068	0.386

BMD: bone mineral density; OR: odds ratio; CI: confidence interval; RA: rheumatoid arthritis; RF: rheumatoid factor; anti-CCP Ab: anti-cyclic citrullinated peptide antibody; DM: diabetes mellitus; BMI: body mass index; DAS28-CRP: disease activity score 28-C-reactive protein; MTX: methotrexate; HCQ: hydroxychloroquine; SSZ: sulfasalazine; LEF: leflunomide; TAC: tacrolimus.
†DAS28-CRP ≤3.2

patients achieved at least low disease activity (DAS28-CRP ≤3.2). The median cumulative dose of glucocorticoid was 1035.0 (540.0–1650.0) mg, which was used in median 266.0 (154.0–365.0) days within the 1-year follow-up period. In terms of type of bisphosphonate, risedronate and alendronate were used in 107 (69.9%) and 46 (30.1%) patients, respectively.

csDMARDs were used in the following proportions: MTX, 84.3%; HCQ, 52.9%; SSZ, 27.5%; LEF, 20.3%; and TAC, 11.1%. Majority of the patients received csDMARDs as a combination therapy (99 of 153 patients, 64.7%) rather than as a monotherapy (54 of 153 patients, 35.3%). The median cumulative dose of MTX, HCQ, SSZ, LEF and TAC was 650.0 (520.0–780.0) mg, 73.0 (44.0–146.0) g, 362.0 (137.0–381.3) g, 3540.0 (2740.0–4625.0) mg, and 313.0 (177.5–557.5) mg, respectively, which was used in median 365.0 (365.0–365.0) days, 365.0 (195.5–365.0) days, 295.0 (100.0–365.0) days, 187.0 (119.0–365.0) days, and 176.0 (133.0–365.0) days, respectively.

Initial T-scores in lumbar spine and femoral neck were -2.9 (-3.4 – -2.6) and -2.2 (-2.8 – -1.6), respectively. Median 1 year % change of BMDs were 3.06 (1.05–7.40)% in lumbar spine and 1.30 (-1.28–3.08)% in femoral neck. Significant BMD increase (ΔBMD ≥3%) in lumbar spine and femoral neck was observed in 87 (56.9%) and 40 (26.1%) patients, respectively.

Factors associated with significant increase of BMD at one year

Logistic regression analysis results for factors associated with increased BMD at one year are presented in Table II (lumbar spine BMD) and Table III (femoral neck BMD). Regarding lumbar spine BMD, the positivity of RF (unadjusted odds ratio (OR) 1.789, 95% confidence interval (CI) 0.859–3.723, p=0.120), BMI (unadjusted OR 0.906, 95% CI 0.821–0.999, p=0.047), HCQ (unadjusted OR 0.646, 95% CI 0.339–1.233, p=0.185), LEF (unadjusted OR 3.211, 95% CI 1.288–8.007, p=0.012), and type of bisphosphonate (risedronate) (unadjusted OR 2.177, 95% CI 1.079–4.395, p=0.030) had p<0.2 on the univariable analysis. On multivariable analysis, the use of LEF remained statistically significant (adjusted OR 3.000, 95% CI 1.177–7.645, p=0.021) (Table II). In terms of femoral neck BMD, no factors were associated with increased BMD at one year (Table III).

Table IV. Factors associated with significantly increased lumbar spine BMD at one year: subgroup analysis on MTX users

Univariable analysis

	Unadjusted OR	95% CI	*p*-value
Female	0.952	0.255 – 3.554	0.942
Age	0.998	0.959 – 1.038	0.915
RA duration	0.997	0.991 – 1.002	0.259
RF	1.605	0.705 – 3.653	0.259
Anti-CCP Ab	1.269	0.520 – 3.100	0.601
DM	1.961	0.495 – 7.765	0.338
BMI	0.939	0.845 – 1.043	0.240
DAS28-CRP	0.944	0.622 – 1.431	0.784
At least low disease activity† at 1 year	1.258	0.398 – 3.981	0.696
Cumulative dose of glucocorticoid	1.009	0.962 – 1.059	0.713
Type of bisphosphonate (risedronate)	1.969	0.924 – 4.196	0.079
HCQ	0.639	0.315 – 1.297	0.215
SSZ	0.955	0.421 – 2.167	0.912
LEF	2.677	1.049 – 6.833	**0.039**
TAC	1.243	0.345 – 4.478	0.740

Multivariable analysis

	Adjusted OR	95% CI	*p*-value
Type of bisphosphonate (risedronate)	1.950	0.903 – 4.212	0.089
LEF	2.653	1.030 – 6.836	**0.043**

BMD: bone mineral density; MTX: methotrexate; OR: odds ratio; CI: confidence interval; RA: rheumatoid arthritis; RF: rheumatoid factor; anti-CCP Ab: anti-cyclic citrullinated peptide antibody; DM: diabetes mellitus; BMI: body mass index; DAS28-CRP: disease activity score 28-C-reactive protein; HCQ: hydroxychloroquine; SSZ: sulfasalazine; LEF: leflunomide; TAC: tacrolimus.
†DAS28-CRP ≤3.2

Table V. Factors associated with significantly increased femoral neck BMD at one year: subgroup analysis on MTX users

	OR	95% CI	*p*-value
Female	0.767	0.181 – 3.248	0.719
Age	1.005	0.962 – 1.050	0.819
RA duration	0.999	0.992 – 1.005	0.678
RF	1.381	0.534 – 3.573	0.506
Anti-CCP Ab	1.614	0.553 – 4.709	0.381
DM	1.518	0.416 – 5.536	0.527
BMI	1.044	0.933 – 1.169	0.452
DAS28-CRP	1.059	0.672 – 1.669	0.804
At least low disease activity† at 1 year	0.590	0.179 – 1.943	0.386
Cumulative dose of glucocorticoid	1.022	0.970 – 1.077	0.410
Type of bisphosphonate (risedronate)	1.258	0.538 – 2.942	0.596
HCQ	1.250	0.576 – 2.711	0.572
SSZ	1.584	0.667 – 3.762	0.297
LEF	0.966	0.383 – 2.434	0.942
TAC	0.174	0.029 – 1.901	0.234

BMD: bone mineral density; MTX: methotrexate; OR: odds ratio; CI: confidence interval; RA: rheumatoid arthritis; RF: rheumatoid factor; anti-CCP Ab: anti-cyclic citrullinated peptide antibody; DM: diabetes mellitus; BMI: body mass index; DAS28-CRP: disease activity score 28-C-reactive protein; HCQ: hydroxychloroquine; SSZ: sulfasalazine; LEF: leflunomide; TAC: tacrolimus.
†DAS28-CRP ≤3.2

Subgroup analysis on MTX users

The results of subgroup analysis are shown in Table IV (lumbar spine BMD) and Table V (femoral neck BMD). In terms of lumbar spine BMD, type of bisphosphonate (risedronate) (unadjusted OR 1.969, 95% CI 0.924–4.196, p=0.079), and LEF (unadjusted OR 2.677, 95% CI 1.049–6.833, p=0.039) had p<0.2 on the univariable analysis. On multivariable analysis, the association between use of LEF and significant increase in lumbar spine BMD was preserved (adjusted OR 2.653, 95% CI 1.030–6.836, p=0.043) (Table IV). In regard to femoral neck BMD, still no factors were associated with significant increase at one year (Table V).

Discussion

In this retrospective study in a cohort of patients with RA who were newly diagnosed with osteoporosis and received bisphosphonate, we note that use of LEF was associated with significant improvement in lumbar spine BMD at one year. To the best of our knowledge, this is the first study to provide clinical data regarding the effect of various csDMARDs on bone mass in RA patients with osteoporosis.

LEF is an isoxasole derivative that inhibits *de novo* pyrimidine biosynthesis by acting on dihydroorotate dehydrogenase (17, 18). It blocks the induction of nuclear factor of activated T cells c1, the master switch regulator for osteoclast differentiation and has a direct inhibitory effect on receptor activator of NF-κB ligand-mediated osteoclast differentiation (8). Although *in vitro* data show that MTX, SSZ, and TAC also have inhibitory effects on osteoclastogenesis (10, 11), our analysis shows that only LEF is associated with significant improvement in lumbar spine BMD.

This may be the result of varying efficacies of different csDMARDs in inhibiting the bone-resorbing function of osteoclasts rather than inhibiting osteoclastogenesis. *In vitro* data have shown that A771726, the active metabolite of LEF, was similar to MTX in its ability to inhibit osteoclastogenesis (9). However, the inhibitory effect on bone-resorbing function of osteoclast was higher in A771726 than in MTX (9). Further, while the inhibitory effect of SSZ and TAC on osteoclastogenesis has been noted (10, 11), their effect on the bone-resorbing activity of osteoclasts is yet to be reported. Notably, in RA, the increased functional activity of osteoclasts rather than increased osteoclast formation is more likely to play a role in bone loss (19, 20). This underlying pathophysiology of bone loss in RA appears to be the basis of the mechanism behind the association of LEF with significant increase in BMD in the present study.

LEF, in our study, was predominantly used as a combination therapy with MTX (29 of 31 patients, 93.5%). Therefore, to exclude confounding by MTX, we performed a subgroup analysis on MTX users. LEF was still significantly associated with significant increase in lumbar spine BMD, suggesting the effect of LEF apart from MTX. However, as only 2 patients (6.5%) received LEF as a monotherapy, it is still unclear whether LEF is also beneficial to lumbar spine BMD when used as a monotherapy.

The cumulative dose of each csDMARD in our study was relatively low. Therefore, if csDMARDs were used in a higher dose, the results may differ. This especially applies to HCQ. Even though one study reported no inhibitory effect of HCQ on osteoclastogenesis (10), another study reported an inhibitory effect of HCQ on both the formation of multinucleated osteoclasts and bone-resorbing activity (21), which suggests that HCQ might have a positive effect on BMD. However, the cumulative dose of HCQ during the one-year follow-up period was relatively low in our study (median 73.0 g (equivalent to 200 mg/day)), and there was no association between the use of HCQ and increased BMD at this dose.

In the present study, the effect of LEF on BMD improvement was observed in the lumbar spine but not in the femoral neck. Furthermore, in the total study population, proportion of patients achieving significant BMD increment in femoral neck was lower compared to that in lumbar spine (26.1% *vs*. 56.9%), and no factors were associated with BMD improvement in femoral neck. This can be explained by the different ratio of cortical to trabecular bone within vertebra and femoral neck. Femoral neck is composed of higher ratio of cortical bone, compared to vertebra (22). As the rate of bone turnover is lower in cortical bone than in trabecular bone (22), higher proportion of cortical bone in femoral neck can explain the less change of BMD in this anatomical site.

Although disease activity and use of glucocorticoids are known risk factors of bone loss in RA (23, 24), DAS28-CRP and cumulative dose of glucocorticoid were not associated with significant BMD change in our study. We presume that this is because DAS28-CRP and cumulative dose of glucocorticoid were relatively low in our cohort patients. Majority of the patients had at least low disease activity (mean DAS28-CRP: 2.53 (±0.86)), and the median cumulative dose of glucocorticoid was 1035.0 (540.0–1650.0) mg (average daily dose lower than 5mg). This is consistent with the previous study, which reported low dose glucocorticoid (mean daily dose 6.6mg) in RA is not associated with an increased risk of bone loss (25).

The present study has some limitations. First, data regarding bone resorptive markers are unavailable. These data, if were present, may have offered a better connection with the data from previous *in vitro* studies. Second, we lack data on vitamin D status. However, as all patients received vitamin D supplementation in a dose of 800 IU/day, we presume that the prevalence of vitamin D deficiency is low in our study population. Third, patients exclusively received bisphosphonate as a treatment for osteoporosis. Therefore, the results in this study cannot be extrapolated to RA patients with osteoporosis receiving other osteoporosis medication (selective oestrogen receptor modulators, denosumab, and teriparatide). Fourth, this study is retrospective in design. Although patients were excluded with strict criteria for homogeneity, and multivariable analysis was performed to reduce the effect of confounders, the confounding effects cannot be fully excluded. Future prospective, controlled studies are warranted for confirming our results.

In conclusion, we have shown that in RA patients with osteoporosis, the use of LEF is associated with significant BMD increment in lumbar spine, whereas other csDMARDs are not. This result suggests that LEF can be beneficial in terms of BMD in RA patients with osteoporosis.

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