Different Effects of Biologics on Systemic Bone Loss Protection in Rheumatoid Arthritis: An Interim Analysis of a Three-Year Longitudinal Cohort Study

Ming-Han Chen1,2†, Shan-Fu Yu3,4†, Jia-Feng Chen3,4, Wei-Sheng Chen1,2, The-Ling Liou1, Chung-Tei Chou1, Chung-Yuan Hsu3,4, Han-Ming Lai3,4, Ying-Chou Chen3,4, Chang-Youh Tsai1,2 and Tien-Tsai Cheng3,4*

1 Division of Allergy-Immunology-Rheumatology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, 2 Faculty of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan, 3 Division of Rheumatology, Allergy, and Immunology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan, 4 School of Medicine, College of Medicine, Chang Gung University, Taoyuan, Taiwan

Objective: To compare changes in bone mineral density (BMD) in rheumatoid arthritis (RA) patients receiving three-year conventional synthetic disease-modifying anti-rheumatic drugs (csDMARD), tumor necrosis factor-α inhibitors (TNFi), and abatacept.

Methods: Patients with RA were recruited from September 2014 to February 2021. Dual-energy X-ray absorptiometry was used to measure BMD at the femoral neck (FN), total hip (TH), and lumbar spine (L1-4) at enrollment and three years later. Changes in the BMD of each regimen group were analyzed. Multiple ordinary least squares regression was used with the dependent variables to develop a model to predict the change in BMD.

Results: A total of 752 participants were enrolled and 485 completed the three-year follow-up period. Of these, 375 (Group I), 84 (Group II), and 26 (Group III) participants received csDMARDs, TNFi, and abatacept therapy, respectively. Considering both type of therapy and completion of the follow-up period, participants were divided into groups A (csDMARDs, n = 104), B (TNFi, n = 52), and C (abatacept, n = 26). Compared to baseline, BMD decreased significantly at FN (p = 0.003) and L1-4 (p = 0.002) in Group A and at L1-4 (p = 0.005) in Group B, but remained stable at all sites in Group C. In terms of regression-adjusted percent change in BMD, there was a significant difference seen at all measured sites between group C compared to both groups A and B (+0.8%, -2.7%, -1.8% at FN; +0.5%, -1.1%, -1.0% at TH; +0.8%, -2.0%, -3.5% at L1-4, respectively; all p < 0.05). Anti-osteoporosis therapy had a BMD-preserving effect in RA.
INTRODUCTION

Rheumatoid arthritis (RA) is one of the most common forms of chronic inflammatory arthritis. This symmetrical polyarthritis mainly affects middle-aged females and leads to progressive joint destruction and loss of function (1). Osteoporosis is characterized by low bone mass, leading to bone fragility as well as a consequent increase in fracture risk (2). It is well known that patients with RA have an increased risk of developing osteoporosis. It has been reported that annual bone loss is greater in patients with active RA than in healthy patients (3). Compared with the general population, a two-fold increase in the frequency of osteoporosis in the spine was observed in RA patients (4). In addition, a meta-analysis revealed that the relative risk for bone fracture was higher among patients with RA than among those without RA (risk ratio 2.25) (5).

In recent years, a greater understanding of immunopathology has facilitated the development of biologic disease-modifying antirheumatic drugs (bDMARDs), which target specific components of the immune response and improve the clinical outcomes of RA (1). Inhibition of pro-inflammatory cytokines, such as tumor necrosis factor-α inhibitor (TNFi), seems to be effective in reducing disease activity and inhibiting bone loss in patients with RA (6–9). CTLA-4 Ig (Abatacept) is a fusion protein that regulates the T-cell co-stimulatory signal and is effective in attenuating disease activity and reducing joint damage in RA patients who have an inadequate response to methotrexate (10, 11). Previous research has demonstrated that abatacept can increase BMD at the femoral neck (FN) and is superior to that of other biologics in patients with RA (12).

In our previous investigation, we demonstrated that three-year biological/targeted synthetic DMARD (b/tsDMARD) treatment can prevent bone loss in RA patients and conventional synthetic DMARD (csDMARD) does not (13). However, the long-term effect in preserving BMD in patients with RA treated with TNFi or abatacept is unknown. The primary aim was to explore the BMD changes in patients with RA treated with csDMARD, TNFi, and abatacept via a three-year, real-world, observational, cohort study. The secondary aim was to investigate the synergistic effect of anti-osteoporosis therapy (AOT) on BMD in patients with RA receiving different therapies.

Abbreviations: ACPA, anti-cyclic citrullinated peptide antibodies; ACR, American College of Rheumatology; AOT, anti-osteoporosis therapy; bDMARD, biologic disease-modifying antirheumatic drug; BMI, body mass index; CRP, C-reactive protein; csDMARD, conventional synthetic DMARD; DAS28-ESR, Disease Activity Score in 28 joints based on erythrocyte sedimentation rate; DKK1, Dickkopf-1; EULAR, European League Against Rheumatism; FN, femoral neck; FRAX, fracture risk assessment tool; L1–4, lumbar vertebrae; RA, rheumatoid arthritis; RANKL, receptor activator of nuclear factor-κB ligand; RF, rheumatoid factor; TH, total hip; TNFi, tumor necrosis factor-α inhibitor; tsDMARD, targeted synthetic DMARD.

Conclusion: Compared with csDMARDs and TNFi, abatacept may have a better BMD-preserving effect in RA. Anti-osteoporosis therapy can prevent systemic bone loss irrespective of RA therapy.

Keywords: rheumatoid arthritis, osteoporosis, bone mineral density, tumor necrosis factor-α inhibitors, abatacept

METHODS

Study Population

This was a multi-center, three-year, real-world, observational cohort study. This study was approved by the Institutional Ethics Committee of Chang Gung Memorial Hospital, Kaohsiung (CGMHK) (approval number: 104-3530B, 106–0047 C) and Taipei Veterans General Hospital (TVGH) (approval number: 2018-04-006BC, 2020-09-013CC) and was conducted in accordance with the guidelines of the Declaration of Helsinki. Informed consent was obtained from all participants. The enrollment criteria included patients with RA who fulfilled the 1987 American College of Rheumatology (ACR) revised criteria (14) or the 2010 ACR/European League Against Rheumatism (EULAR) classification criteria (15), visited the rheumatology clinic at these two medical centers since September 2014, and received csDMARD, TNFi, or abatacept following the National Institute for Health and Care Excellence guidelines during the three-year observation period.

Bone Mineral Density

The BMD at the FN, hip (total) (TH), and lumbar vertebrae 1–4 (L1–4) of each participant were measured using dual-energy X-ray absorptiometry scanners (CGMHK, Delphi A; Hologic Corp., Waltham, MA, USA; TVGH, QDR 4500A; Hologic Inc., Waltham, MA, USA) upon enrollment and three years later.

Clinical and laboratory assays of the RA patients were recorded upon enrollment, including age, sex, body height, body weight, body mass index (BMI), and the presence of rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (ACPA). RA disease activity was measured using C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and Disease Activity Score in 28 joints based on ESR (DAS28-ESR) (16). Information on current medications at the time of enrollment was collected. In addition, risk factors for fragility fractures based on the FRAX tool were recorded. Considering all of these, the 10-year probabilities of major and hip fractures were calculated and recorded. Prescription of oral systemic glucocorticoids was recorded at baseline and during the study period, and was converted to a prednisolone equivalent dose. Baseline exposure was defined as current glucocorticoid usage of > 3 months before enrollment, noting and calculating the mean daily dose within the last three months. The mean daily dose of glucocorticoids during the observation period was determined by this equation: cumulative dose of glucocorticoid prescribed ÷ cumulative dispensing days during the three-year observation period.
Statistical Analysis

Independent Student’s t-test was used to compare numerical data that exhibited normal distribution and Mann–Whitney U test was used for data that showed otherwise. Categorical variables were evaluated with chi-square test or Fisher’s exact test. Change in BMD of each participant from baseline was calculated using paired t-test. A one-way ANOVA or Kruskal-Wallis test was used to determine the significant difference between the three treatment groups in terms of parametric data. Multiple ordinary least squares (OLS) regression was used to assess the independent effects of drug treatment on the three dependent variables, controlling for age, gender, BMI (> or ≤ 24), disease duration, ACPA positivity, and baseline DAS28-ESR (> or ≤ 3.2), based on which the predicted value of the changes in BMD was calculated. Data are presented as mean ± SD or median (interquartile range, IQR) for normal and non-normal distribution datasets. The p-value was two-tailed and interpreted as significant when the value was < 0.05. Statistical analyses were performed using SPSS version 22.0 (IBM SPSS Statistics for Windows, IBM, Armonk, New York, USA).

RESULTS

Patients

A total of 752 participants were registered from September 2014 to February 2021, but only 485 participants completed the three-year follow-up period by the end of February 2021. The
disposition of the participants is illustrated in Figure 1; 188 patients lost to follow-up or followed less than 3 years since enrollment, while 79 patients received TNFi or abatacept less than 1 year or switched to another biologic agent with a different mechanism of action during observation period.

The demographics and clinical characteristics of the enrolled patients are shown in Table 1. Eligible participants were grouped into group I (n = 375, csDMARD), II (n = 84, TNFi, including etanercept, adalimumab, and golimumab), and III (n = 26, abatacept) or by regimens used during the observation period. Mean age and sex were not significantly different between the groups. The characteristics of RA disease entities were not obviously different among groups except for baseline disease activity (DAS28-ESR) (p < 0.001), three-year mean DAS28-ESR (p = 0.014), rate of positive RF (p = 0.001), rate of positive ACPA (p = 0.002), baseline glucocorticoid exposure (p < 0.001), and rate of cumulative exposure to glucocorticoids (p = 0.001). In addition, baseline BMD and risk factors for fragility fractures in the FRAX tool were comparable among the groups.

Matching the rate of glucocorticoid use across groups I to III to a ratio of 4:2:1, the groups were subdivided into groups A (n = 104, csDMARD), B (n = 52, TNFi), and C (n = 26, abatacept), respectively. The demographic and clinical characteristics of the participants are shown in Table 2. Mean age and sex were not significantly different between the groups. Body mass index was significantly different (p = 0.023). The characteristics of RA disease entities were not obviously different among groups except for baseline disease activity (DAS28-ESR) (p < 0.001), three-year mean DAS28-ESR (p = 0.004), and rate of positive ACPA (p = 0.013). The baseline BMD and risk factors for fragility fracture in the FRAX tool were comparable among groups after matching. Fifty-seven patients received AOT; 44,
5, 4, and 1 patient treated with bisphosphonate, denosumab, selective estrogen receptor modulators (SERM), and teriparatide alone, while one patient in group B received denosumab and teriparatide, another one patient in group B received bisphosphonate and SERM, and one patient in group C received bisphosphonate and denosumab during observation period. There was no significant difference in the percentage of patients on bisphosphonate, denosumab, and teriparatide between different groups, while more patients in group B received SERM when compared to those in other groups.

### Comparison of BMD Changes With Baseline After Matching

Comparing baseline values of all participants, BMD at FN and L1-4 significantly decreased in group A (p = 0.003 and 0.002, respectively) (Table 3 and Figure 2A). Although BMD of L1-4 significantly decreased in group B (p = 0.005), there were no significant changes seen at the three measured sites in group C. Changes in BMD in participants who received AOT are shown in Table 3 and Figures 2B, C. BMD at FN, TH, and L1-4 in participants who received AOT remained stable in the three groups. An exemption to this was BMD at FN, which significantly increased compared to baseline in group C (p = 0.012). Participants in group A and without AOT showed significant declines in BMD at FN, TH, and L1-4 (p = 0.003, 0.027, and < 0.001, respectively) (Figure 2C). BMD of group B participants without AOT revealed a significant decline at L1-4 (p = 0.010). BMD of group C participants without AOT remained stable at FN, TH, and L1-4 (p = 0.530, p = 0.888, and p = 0.741, respectively (Figure 2C).

### TABLE 2 | Demographics and clinical characteristics of participants, after matching.

| Group | N = 182 | A n = 104 | B n = 52 | C n = 26 | p f |
|-------|---------|----------|----------|--------|------|
| Age (years) | 57.5 ± 10.7 | 57.7 ± 10.5 | 58.1 ± 10.2 | 55.3 ± 12.8 | 0.531 |
| Female, n (%) | 159 (87.4) | 93 (89.4) | 43 (82.7) | 23 (88.5) | 0.500 |
| Body weight (kg) | 58.2 ± 10.6 | 56.8 ± 9.6 | 61.8 ± 12.6 | 56.7 ± 8.5 | 0.016* |
| Body height (cm) | 157.4 ± 6.5 | 156.8 ± 6.8 | 158.1 ± 5.6 | 158.2 ± 6.9 | 0.425 |
| BMI (kg/m²) | 23.6 ± 3.7 | 23.0 ± 3.3 | 24.7 ± 4.6 | 22.8 ± 2.9 | 0.023* |

Data are presented as mean ± standard deviation, or median (interquartile range). Defined as in FRAX tool.

*Defined as number and proportion (%) of patients who had ever received glucocorticoid therapy during the 3-year observation period.

**Defined as a T-score equal to −2.5 or less at femoral neck.

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TABLE 3 | Comparison of BMD between baseline and 3 years later in each treatment group, after matching.

| Group | AOT + | AOT - |
|-------|-------|-------|
| FN    |       |       |
| base  | 0.632 ± 0.113 | 0.644 ± 0.129 | 0.598 ± 0.107 |
| 3-y   | 0.557 ± 0.072 | 0.560 ± 0.071 | 0.531 ± 0.076 |
| base  | 0.655 ± 0.113 | 0.687 ± 0.132 | 0.638 ± 0.104 |
| TH    |       |       |
| base  | 0.791 ± 0.119 | 0.802 ± 0.162 | 0.744 ± 0.123 |
| 3-y   | 0.722 ± 0.110 | 0.723 ± 0.116 | 0.669 ± 0.116 |
| base  | 0.812 ± 0.114 | 0.842 ± 0.170 | 0.790 ± 0.106 |
| L1-4  |       |       |
| base  | 0.858 ± 0.149 | 0.906 ± 0.175 | 0.856 ± 0.134 |
| 3-y   | 0.758 ± 0.123 | 0.799 ± 0.120 | 0.766 ± 0.104 |
| base  | 0.891 ± 0.142 | 0.977 ± 0.170 | 0.907 ± 0.124 |

AOT+, received anti-osteoporosis therapy; AOT-, did not receive anti-osteoporosis therapy; base, baseline; BMD, bone mineral density; 3-y, 3 years later; FN, femoral neck; L1-4, lumbar vertebrae 1-4; TH, total hip.

Data are presented as mean ± standard deviation.

*A, csDMARD; B, TNF; C, abatacept;
*BMD comparison between baseline and 3 years later.

Differences in Percent Change of BMD Among Groups After Matching

After three years, percent changes in BMD (ΔBMD%) at FN and TH were not significantly different among groups except at L1-4 (p = 0.026) after matching in all participant groups (Table 4 and Figure 3A). ΔBMD% at L1-4 in group C was significantly different from that in group A (both p < 0.05), while the regression-adjusted ΔBMD% at FN became less statistically different among participants with AOT (p = 0.053).

DISCUSSION

Current investigation demonstrated that AOT can prevent bone loss irrespective of regimen used, while in patients without AOT, participants who received csDMARD had the most obvious bone loss at all sites. Participants who received abatacept therapy demonstrated stable BMD at all sites, irrespective taking AOT therapy or not. This investigation revealed that abatacept may have a better systemic bone loss protection effect in RA patients than the other two regimens.

The b/tsDMARD not only demonstrated better control of disease activity, but also showed a better bony erosion protection effect than csDMARD in RA patients (17–26). Our previous investigation revealed that long-term b/tsDMARD therapy demonstrated a potentially beneficial effect on the protection of systemic bone loss (13). However, previous investigations regarding the effect of biologics on the prevention of systemic bone loss in RA have only focused on changes in bone turnover markers (18–21), over a short-term observation period (25, 26), and with a lack of an adequate control group (25, 27). In addition, the long-term effects of bDMARDs with different mechanisms of action on systemic bone loss in patients with RA remain obscure.

CTLA-4 is a negative regulator that inhibits antigen-specific immune responses after T-cell activation by interfering with the interaction of CD28 on T-cells and CD80/86 on antigen-
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As the current study is a real-world investigation, we did not exclude participants who received AOT during the observation period to elucidate the interaction of DMARD therapy and AOT in terms of bone protective effects. Participants who did not receive AOT had significant bone loss at all sites in group A and at the lumbar vertebrae in group B. AOT had a protective effect against bone loss in all groups at all sites. These results suggest that AOT plays the most important role in bone loss protection in RA patients receiving either csDMARD or biologics.

A strength of the current investigation is that it is a longitudinal, real-world, observational, registry, cohort study. We measured and recorded the characteristics of the disease entity at baseline and serial disease activity, which could potentially influence BMD changes during the study period. In addition, most previous studies were single-arm studies without an adequate control group (25, 27). Our initial investigation revealed a significant difference in the rate of glucocorticoid use among groups. As glucocorticoid use is a well-known risk factor for bone loss, we performed a 4:2:1 matching for glucocorticoid use to exclude the confounding effect of glucocorticoids, which had not been done in previous investigations. Furthermore, to adjust confounders of osteoporosis, multiple regression analysis was used to develop a model to predict the change in BMD. Finally, this study is the first investigation to explore the long-term systemic bone loss protective effect among DMARDs with different mechanisms of action to elucidate the effects of biologics on RA patients.

The current study has some limitations. As it was a real-world study, we did not exclude participants who had already received biologics before enrollment. Hence, we could not exclude the residual effect of previous medications on BMD after enrollment. However, we excluded participants with biologic switching during the observation period to avoid additional confounding effects. In addition, we did not compare the bone loss protective effect between abatacept and biologics other than TNFi, eg. tocilizumab, rituximab. So far, we could not know which biologics is the best one to prevent bone loss in RA patients. Fracture prevention is a hard outcome to measure in osteoporosis studies, and we could not compare the effect of fracture prevention among the treatment groups owing to the short duration and relatively small sample size of our study.

### Table 4

| Group          | A°   | B°   | C°   | N  | △BMD %b  | P°   |
|----------------|------|------|------|----|----------|------|
| **Total**      |      |      |      |    |          |      |
| unadjusted     | -1.6 (8.5) | -2.5 (3.8) | 0.3 (10.4) | 0.146 |
| adjusted       | -2.7 (2.0)  | -1.8 (2.1)  | 0.8 (12.2)  | <0.001 |
| TH             | 101   | 41   | 24   |    |          |      |
| unadjusted     | -1.2 (12.7) | -0.4 (9.1)  | 0.3 (8.4)   | 0.790  |
| adjusted       | -1.1 (1.6)  | -1.0 (1.9)  | 0.5 (18.8)  | <0.001 |
| L1-4           | 99    | 50   | 25   |    |          |      |
| unadjusted     | -2.0 (7.7)  | -2.5 (8.6)  | 3.2 (7.6)   | 0.026  |
| adjusted       | -2.0 (2.0)  | -3.5 (2.7)  | 0.8 (19.9)  | <0.001 |
| AOT °          |      |      |      |    |          |      |
| unadjusted     | 1.1 (6.1)   | -4.0 (16.9) | 4.1 (7.0)   | 0.083  |
| adjusted       | -3.0 (1.7)  | -2.2 (1.8)  | 0.5 (9.9)   | <0.001 |
| TH             | 24    | 14   | 9    |    |          |      |
| unadjusted     | 1.2 (14.0)  | -2.2 (8.8)  | 1.9 (15.9)  | 0.356  |
| adjusted       | -1.1 (1.4)  | -1.2 (1.4)  | 0.5 (10.0)  | 0.005  |
| L1-4           | 25    | 20   | 1.9  |    |          |      |
| unadjusted     | 0.8 (10.1)  | -4.3 (11.7) | 3.2 (6.6)   | 0.232  |
| adjusted       | -2.2 (2.7)  | -3.6 (2.4)  | 0.3 (6.6)   | <0.001 |
| AOT °          |      |      |      |    |          |      |
| unadjusted     | -2.7 (8.9)  | -1.5 (8.2)  | -2.1 (8.6)  | 0.246  |
| adjusted       | -2.7 (2.0)  | -1.8 (2.1)  | 0.8 (12.2)  | <0.001 |
| TH             | 77    | 27   | 15   |    |          |      |
| unadjusted     | -2.0 (12.7) | 0.1 (11.3)  | -0.1 (7.9)  | 0.478  |
| adjusted       | -1.1 (1.6)  | -1.0 (1.9)  | 0.5 (18.8)  | 0.014  |
| L1-4           | 74    | 30   | 16   |    |          |      |
| unadjusted     | -2.4 (7.3)  | -1.8 (9.1)  | 2.8 (8.1)   | 0.068  |
| adjusted       | -2.0 (2.0)  | -3.5 (2.7)  | 0.8 (19.9)  | <0.001 |

AOT+, received anti-osteoporosis therapy; AOT−, did not receive anti-osteoporosis therapy; FN, femoral neck; L1-4, lumbar vertebrae 1-4; TH, total hip BMD, bone mineral density; FN, femoral neck; L1-4, lumbar vertebra 1-4; TH, total hip.

Data are presented as median (interquartile range).

A°, csDMARD; B°, TNFi; C°, abatacept.

△BMD%: [(BMD 3 years later − BMD at baseline)/BMD at baseline] × 100%.

Comparison of △BMD% among groups at each site

Predicted change in BMD was calculated by multiple regression analysis after adjusting age, gender, BMI (> or ≦ 24), disease duration, anti-cyclic citrullinated peptide antibody positivity, and baseline DAS28-ESR (> or ≦ 3.2).
CONCLUSION

RA patients receiving long-term abatacept illustrated a better bone loss protective effect than patients receiving csDMARD or TNFi. Anti-osteoporosis therapy has a vital protective effect on bone loss irrespective of regimens for RA therapy used. Further studies are needed to clarify whether abatacept or other biologics could prevent fragility fractures in patients with RA.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Chang Gung Memorial Hospital, Kaohsiung and Taipei Veterans General Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Study concept: M-HC and T-TC. Study design: M-HC, S-FY, and T-TC. Data analysis: M-HC, S-FY, T-TC. M-HC, S-FY, J-FC, W-SC, T-LL, C-TC, C-YH, H-ML, Y-CC, C-YT, and T-TC were responsible for interpretation of the data and for drafting and revising the manuscript. All authors contributed to the article and approved the submitted version.

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