The impact of long-term biologics/target therapy on bone mineral density in rheumatoid arthritis: a propensity score-matched analysis

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Abstract

Objectives. To investigate changes in BMD in RA patients receiving 3-year biological/targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARD) or conventional synthetic DMARD (csDMARD).

Methods. Patients with RA were recruited from September 2014 until March 2019. Clinical characteristics, BMD and evidence of fragility fractures at enrolment were documented. Participants were treated according to the National Institute for Health and Care Excellence (NICE) guidelines over a 3-year observation period. Repeated BMD was measured at the end of the study period. Participants were grouped into those receiving b/tsDMARD or csDMARD and by propensity score matching (1:2).

Results. A total of 388 participants completed the 3-year follow-up. After propensity score matching, 92 and 184 participants were allocated to the b/tsDMARD (Group I) and csDMARD (Group II), respectively. After 3 years, BMD remained stable at the femoral neck (FN), hip (total) (TH) and lumbar vertebra (L1-4) (P = 0.09, 0.15, 0.87) in Group I. However, BMD decreased significantly in Group II (P = 0.045, <0.001, 0.004) at corresponding sites. Participants receiving combined b/tsDMARD and anti-osteoporosis therapy experienced a greater BMD preserving effect than other subgroups.

Conclusion. Long-term b/tsDMARDs therapy had protective effects on bone loss for patients with RA. Patients receiving concomitant anti-osteoporosis therapy and b/tsDMARDs therapy experienced the greatest BMD preserving effect.

Key words: rheumatoid arthritis, biological therapies, bone, osteoporosis, DMARDs

Introduction

RA, an autoimmune disease primarily affecting peripheral joints, also leads to deteriorated skeletal microarchitecture and bone strength. This deterioration is due to the release of proinflammatory cytokines such as TNF-α, IL-6 and IL-17, which interferes with the balance between bone formation by osteoblasts and resorption by osteoclasts. The chronic inflammation in RA not only results in peripheral bony erosion but in generalized bone loss. It has been demonstrated that the annual bone loss rate in patients with active RA ranges between 5.5% and 10% [1]. Compared with the general population, the prevalence of osteoporosis is approximately two-fold greater in patients with RA [2], ranging from 7% to 26% in the hip and 11% to 32% in the spine [2–5]. In addition, the risk of developing clinical or hip/vertebral fractures in patients with RA has been reported to be 2.25 or 2–6 fold, respectively, and was higher than that of controls [6].

Rheumatology key messages

- Long-term b/tsDMARDs benefit RA patients not only in ameliorating disease activity but also preserving bone mass.
- RA patients who underwent csDMARDs, compared to b/tsDMARDs, experienced more substantial bone loss.
In recent decades, several cytokines inhibitors, in particular biological/targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARD) have been developed. The b/tsDMARD therapy directly targets pathological cytokines and halts the inflammatory cascade and has demonstrated anti-inflammatory effects for patients with RA. Since the advent of b/tsDMARDs, the regimens have demonstrated marked clinical symptom alleviation, improved quality of life, and decelerated joint damage in patients with RA. In addition, the notion of treat-to-target strategy accelerated the optimisation of patient management and outcomes [7].

In previous studies [8–13], b/tsDMARDs had demonstrated a potentially beneficial effect on bone loss. However, these studies either focused on changes in bone turnover markers, [10–13] had a short-term observation period, [8, 14–17] or lacked an adequate control group [8, 9]. Therefore, the long-term effect of b/tsDMARDs on generalized bone loss in patients with RA remained unknown. Medications for the treatment of postmenopausal osteoporosis including denosumab, bisphosphonates and parathyroid hormone (hPTH 1–34) have been assessed in terms of preventing bone loss in patients with RA. They have demonstrated efficacy in the prevention of systemic bone loss or in reducing localized bone erosions [18–20].

In the current study, we aimed to investigate the impact of long-term b/tsDMARDs therapy on BMD changes in patients with RA via a 3-year real-world, prospective, cohort and observational study. In addition, we explored the synergistic effect of a 3-year treatment with b/tsDMARDs and with or without anti-osteoporosis therapy (AOT) on BMD changes in patients with RA.

Methods
Study population
The inclusion criteria for participants and the methods for the current study have been previously published [21]. In brief, this was an interim analysis of an RA-related osteoporosis/fracture registry study conducted at Chang Gung Memorial hospital, Kaohsiung (CGMHK), Taiwan. In the registry, consecutive patients with RA who fulfilled the 1987 ACR revised criteria [22] or the 2010 ACR/European League Against Rheumatism (EULAR) classification criteria [23] and who had visited the rheumatology clinic at CGMHK since 1 September 2014, were enrolled. We excluded subjects who were <20 years of age, had any malignancy during the previous 5 years, or were unwilling to join in the study.

Clinical assessments included demographic data, presence of anti-cyclic citrullinated peptide antibodies (anti-CCP) and RF. Disease duration was defined as the time elapsed between the onset of the first disease-related symptoms and enrolment in the study. RA activity was assessed using the DAS in 28 joints based on ESR (DAS28-ESR). Information on current medications at the time of registration was collected. In addition, lifestyle factors, evidence of previous fragility fractures (history or radiographic), and risk factors for fragility fracture based on the FRAX® tool were recorded. The 10-year probability of major and hip fractures was calculated and recorded. Prescription of systemic glucocorticoid (oral, intravenous, subcutaneous or intramuscular administration) was recorded at baseline and during the study period, converting to a prednisolone-equivalent dose. We defined baseline exposure as current steroid usage at the start date of study for >3 months or having been exposed for >3 months before the start date, and calculated the average dose within the latest 3 months. Cumulative exposure was defined as any systemic glucocorticoid exposure during the study cohort, and the cumulative dose was determined at the end of study, recording all the available, systemic glucocorticoid prescription and changing to daily, prednisolone-equivalent dose.

The BMD of each patient was measured at enrolment using a dual-energy X-ray absorptiometry scanner (Delphi A; Hologic Corp., Waltham, MA, USA) for femoral neck (FN), hip (total) (TH) and lumbar vertebra (L1–L4). Body height, body weight and BMI were recorded at baseline. And DAS28-ESR, laboratory assessments for each participant were documented every 3–6 months during the 3-year observation period. Repeated BMD measurements and radiographs at the same site as enrolment were performed for each participant at the end of the 3-year observation period. Each image was read by an independent radiologist, according to Genant’s semiquantitative assessment of vertebral fractures [24] to assess the evidence of vertebral compression fracture at enrolment and 3 years later. Data ceased to be collected on 19 March 2019. During the study period, participants were treated according to National Institute for Health and Care Excellence (NICE) guidelines or 2013/2016 ACR/EULAR recommendations targeted at sustaining low disease activity or remission [25, 26]. Those who completed the 3-year study period were recruited for the analysis.

The participants were grouped based on medications used in the study period. Those who received continuous b/tsDMARDs therapy for at least one year were in the b/tsDMARD group, while those who did not receive any b/tsDMARDs and took only csDMARDs was categorized into the csDMARDs group. In this study, b/tsDMARDs included anti-TNFα (etanercept, adalimumab, golimumab, certolizumab), anti-IL6 receptor (tocilizumab), CTLA4 analogue (abatacept), anti-CD 20 (rituximab) and JAK inhibitor (tofacitinib). The csDMARDs included methotrexate, sulphasalazine, hydroxychloroquine, azathioprine and leflunomide. The propensity score for each participant was calculated based on imbalanced covariates between the b/tsDMARD and csDMARDs groups by logistic regression. Participants were then matched by using an optimal method with a 0.2 calliper width to create 1:2 (b/tsDMARD: csDMARDs) matched groups using NCSS software (NCSS 9; NCSS statistical software, 2013, Kaysville, Utah, USA). Each participant provided written
follow-up and were enrolled in this study. A total of 388 participants completed the 3-year outcome. A total of 651 participants were registered for the study with informed consent and the study was conducted with the approval of the Regional Ethical Review Board of CGMHK(106-0047 C).

Statistics and propensity score matching

Continuous variables were analysed using Student’s t test and the Mann–Whitney U test, whereas categorical variables were evaluated by the Chi-squared test or Fisher’s exact test. P-values < 0.05 were considered statistically significant. The change in BMD of each participant from baseline was calculated by paired t test. We performed the statistical analyses using the Statistical Package for the Social Sciences (SPSS, version 20.0, Chicago, IL, USA). Trend analyses of BMD changes were achieved by one-way analysis of variance (ANOVA) under each category of treatment regimen.

Results

A total of 651 participants were registered for the study cohort. A total of 388 participants completed the 3-year follow-up and were enrolled in this study. The characteristics of the participants are shown in Fig. 1. Before propensity score matching (PSM), there were 102 participants allocated to the b/tsDMARD group, and 286 were allocated to the csDMARD group. The baseline demographics and clinical characteristics of the participants allocated to the b/tsDMARD group, and 286 participants allocated to the csDMARD group. The baseline demographics and clinical characteristics of the participants allocated to the b/tsDMARD group.

Changes in BMD between groups

Compared with baseline, the BMD at FN, TH and L-1-4 after 3 years in Group I exhibited non-significant changes (P = 0.15, P = 0.87, P = 0.09, respectively). The BMD of participants in Group II revealed significant bone loss at FN, TH and L-1-4 (P < 0.001, P = 0.004, P = 0.045, respectively). (Fig. 2)

The changes in BMD in participants of both groups who did or did not receive AOT is shown in Figs 3A and 3B. Compared with baseline, the BMD of the non-users of AOT in Group I participants remained stable at TH, but declined substantially at the FN and L-1-4 (P = 0.046, P = 0.004, respectively). However, non-users of AOT in Group II demonstrated significant BMD reduction at FN, TH and L-1-4 (all P < 0.001) (Fig. 3A). BMD at three measured sites remained stable or slightly increased in participants who received AOT in both groups, irrespective of the use of b/tsDMARD (Fig. 3B).

The subgroup analysis revealed that participants in Group II who did not receive AOT (Group II/AOT–) demonstrated clear bone loss at the FN (~2.8%), TH (~2.3%) and L-1-4 (~2.4%) than the other subgroups (Group I/AOT+, Group II/AOT+ and Group II/AOT–) (Fig. 4A, B and C). As demonstrated in Fig. 4, there was a trend that participants who received b/tsDMARD alone, AOT alone, or combined therapy had progressively better bone loss protection at all skeletal sites than those without either therapy. This phenomenon was most outstanding at FN and L-1-4 (P for trend = 0.018 and 0.001, respectively).

Discussion

This 3-year observational cohort study revealed that b/tsDMARDs preserved BMD at the FN, TH and L-1-4, whereas participants taking csDMARD experienced substantial BMD loss compared with baseline. Several studies have reported the effect of various biologics, mainly anti-TNF, on serial BMD changes in patients with RA [8, 10–17, 27–30]. However, previous studies had a short observation period (1–2 years) [8, 14–17], a small sample size [8, 11, 29], were retrospective in character [30], had no parallel control group [8, 27, 28], or studied the changes in bone markers instead of actual BMD [10–13]. To overcome these limitations, we conducted this prospective, longitudinal, observational, real-world, controlled PSM study.

Despite the limitations of the previous studies, biologic therapy for RA either increased BMD [8, 30] or at
least had a non-detrimental effect on BMD [31, 32] compared with baseline. Krieckaert et al. showed that after 1 year of adalimumab treatment, BMD of the hip and lumbar spine remained stable [33]. Marotte et al. also demonstrated that BMD at the spine and FN did not change after one year of infliximab treatment [34]. However, previous studies provided inconclusive evidence of the impact on BMD of b/tsDMARDs with different mechanisms of action.

Consistent with previous studies on anti-TNFs, our investigation revealed that participants in Group I demonstrated no substantial BMD loss from baseline after 3 years.
However, Group II participants experienced substantial bone loss at the FN (P < 0.001), hip (total) (P = 0.004) and L1-4 (P = 0.04). This finding suggests that long-term b/tsDMARD therapy can protect against generalized osteoporosis in patients with RA better than csDMARD therapy.

In addition to strict control of disease activity by b/tsDMARD therapy, which might arrest generalized bone loss, bisphosphonate [35, 36] and denosumab [37] also demonstrated a protective effect against bone loss on patients with RA. As current study is a real-world investigation, we did not exclude participants who received AOT during the observation period to elucidate the interaction of b/tsDMARD therapy and AOT in terms of bone protective effects. As demonstrated in Fig. 3A, Group II

### Table 1: Clinical characteristics of participants before and after propensity score match (PSM)

|                              | Groups (before PSM) | Groups (after PSM) |
|------------------------------|----------------------|--------------------|
|                              | b/tsDMARD + csDMARD  | csDMARD            |
|                              | n = 102              | n = 286            |
| Age (years)                  | 56.4 (9.4)           | 59.2 (10.2)        | 0.02* |
| Female, n (%)                | 87 (85.3)            | 247 (86.4)         | 0.87 |
| Menopause, n (%)             | 69 (79.3)            | 206 (83.4)         | 0.40 |
| Body weight (kg)             | 60.4 (11.6)          | 57.4 (11.7)        | 0.03* |
| Body height (cm)             | 158.0 (7.0)          | 155.9 (7.4)        | 0.01* |
| BMI (kg/m²)                  | 24.1 (4.0)           | 23.5 (3.9)         | 0.23 |
| Comorbidity*                 | 56 (54.9)            | 189 (66.1)         | 0.04* |
| RA related factors           |                      |                    |      |
| Disease duration (years)     | 15.3 (9.5)           | 14.1 (8.9)         | 0.25 |
| DAS28-ESR                    | 3.7 (1.3)            | 3.1 (1.1)          | 0.001* |
| Cumulative exposure +, n (%) | 79 (77.5)            | 176 (61.8)         | 0.005* |
| CRP (mg/l)                   | 7.2 (13.8)           | 7.5 (15.7)         | 0.86 |
| HAQ-DI                       | 6.1 (6.1)            | 4.6 (6.0)          | 0.04* |
| FRAX risk factorsb           |                      |                    |      |
| Previous fracture +, n (%)   | 28 (27.5)            | 101 (35.3)         | 0.15 |
| 2nd Osteoporosis +, n (%)    | 3 (2.9)              | 14 (4.9)           | 0.58 |
| Glucocorticoida              |                      |                    |      |
| Baseline exposure +, n (%)   | 87 (85.3)            | 251 (87.8)         | 0.50 |
| Dose (mg/day)                | 4.9 (1.0)            | 4.5 (1.9)          | 0.05* |
| Cumulative exposure +, n (%) | 97 (85.1)            | 270 (94.4)         | 1.00 |
| Cumulative dose (mg/day)     | 4.0 (2.5)            | 4.2 (2.3)          | 0.47 |
| Parent fractured hip +, n (%)| 8/102 (7.8)          | 27/282 (9.6)       | 0.006* |
| BMD (g/cm²)                  |                      |                    |      |
| FN                           | 0.784 (0.144)        | 0.785 (0.136)      | 0.92 |
| TH                           | 0.630 (0.115)        | 0.626 (0.117)      | 0.81 |
| L1-4                         | 0.901 (0.171)        | 0.847 (0.161)      | 0.005* |
| Current smoking +, n (%)     | 5 (4.9)              | 18 (6.3)           | 0.61 |
| Alcohol +, n (%)             | 1 (1.0)              | 4 (1.4)            | 1.00 |
| AOT +, n (%)                 | 30 (29.4)            | 102 (35.7)         | 0.25 |
| Laba                         |                      |                    |      |
| Calcium (mg/dl)              | 9.3 (0.3)            | 9.3 (0.4)          | 0.90 |
| Vit D25(OH) (ng/ml)          | 22.1 (7.9)           | 22.7 (7.4)         | 0.54 |
| iPTH (pg/ml)                 | 40.9 (19.9)          | 44.0 (22.8)        | 0.23 |

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*Specific items refer to Supplementary Material, available at Rheumatology online. bDefined as in FRAX tool (www.sheffield.ac.uk/FRA/index.aspx?lang=en). cGroup I: b/tsDMARDs + csDMARD; Group II: csDMARD. dSystemic glucocorticoid (oral, intravenous, subcutaneous or intramuscular administration) was captured as prednisolone-equivalent dose. We define baseline exposure as current steroid usage at the start date of study for >3 months or had been exposed for >3 months before the start date, and calculate the average dose within the latest 3 months. Cumulative exposure was defined as any systemic glucocorticoid exposure during the study cohort, and the cumulative dose was determined at the end of study, recording all the available, systemic glucocorticoid prescription and calculating daily dose. *P-value < 0.05. DAS28-ESR: disease activity score in 28 joints with ESR; HAQ-DI: health assessment questionnaire disability index; AST: aspartate aminotransferase; ALT: alanine transaminase; ALK-P: alkaline phosphatase; iPTH: intact parathyroid hormone. Anti-TNF: including etanercept, adalimumab, golimumab and opiniert. FN: femoral neck; AOT: anti-osteoporosis therapy, including bisphosphonate(s), denosumab, teriparatide, selective oestrogen receptor modulator (SERM); PSM: propensity score match.
participants who did not receive AOT had clear bone loss at all sites \((P < 0.001)\), while, those in Group I who did not receive AOT experienced a protective effect against bone loss only at the hip (total) but not the FN \((P = 0.046)\) or L1-4 \((P = 0.004)\). On the other hand, AOT had a protective effect against bone loss in both groups at all sites (Fig. 3B). These results suggest that AOT plays the most important role in bone loss protection for patients with RA receiving either b/tsDMARD or csDMARD therapy.

In terms of combination therapy, although certain studies [33, 38] enrolled patients with RA who were treated with biologics and concomitant anti-osteoporosis medications, they did not discuss the interaction effect between b/tsDMARD and AOT on protection against bone loss. In the current investigation, the magnitude of percentage changes in BMD loss \((\Delta BMD\%)\) at the FN by groups was as follows: b/tsDMARD+ /AOT+ > csDMARD+ /AOT+ > b/tsDMARD+ /AOT- > csDMARD+ /AOT- \(P\) for trend = 0.018 (Fig. 4A). There was a similar trend at TH \(P\) for trend = 0.06 and L1-4 \(P\) for trend = 0.001 (Figs 4B and C) for these four therapy combinations. To the best of our knowledge, ours is the first study to reveal the additive effect of b/tsDMARD and AOT on the prevention of bone loss in patients with RA. Our results suggest that co-administration of b/tsDMARD and AOT has a better protective effect against generalized bone loss in patients with RA than either b/tsDMARD or AOT alone.

It has been proposed that the anti-inflammatory character of glucocorticoids and b/tsDMARD drugs underlies the protective effects against bone loss in patients with early RA [39, 40]. In the current study, the mean baseline DAS28-ESR and mean 3-year DAS 28-ESR were 3.7 (1.4) and 3.3 (1.0) \(P < 0.001\) in Group I participants, while it was 3.2 (1.1) and 3.1 (0.9) \(P = 0.08\) in Group II participants. Given Group I participants demonstrated less bone loss at all sites than those in Group II at the 3-year follow-up (Fig. 2), the anti-inflammatory character of b/tsDMARD likely played an essential role in protecting against bone loss not only in early RA but also in established RA after 3 years of therapy. Several cytokines, including TNF\(\alpha\), IL-1, IL-6 and IL-17 had activating effect on osteoclast differentiation and proliferation [41]. The b/tsDMARDs could counteract the effect of cytokines on bone through various mechanisms in patients with RA. Whether long-term b/tsDMARDs therapy has a direct inhibitory effect on osteoclastogenesis,
which then mediated the bone loss in patients with RA, is not yet known.

Several studies have suggested that low-dose glucocorticoids have a negative on bone metabolism, but this effect might be nullified by the assistance of the suppression of inflammatory cytokines, particularly in early RA [42]. On the other hand, glucocorticoids have been proposed as a risk factor for bone loss in patients with RA who are receiving biologics [38]. Therefore, to investigate the effect of b/tsDMARD on bone loss protection, we must consider the effect of glucocorticoids. In the current study, when considering possible confounding factors, we made use of PSM to retrieve the control group (Group II) to eliminate the confounding factors, including use and dosage of glucocorticoids. However, although the use and dosage of glucocorticoids was considered, it did not show a substantial effect on bone loss in either group (data not shown).

As mentioned, the observation period of most studies investigating the effect of biologics on bone loss in RA was 1–2 years, and most reassessed BMD after a 1-year follow-up [8, 11, 29, 31]. As suggested by Orsolini et al. [43] the time interval of the follow-up assessment must be long enough to determine whether any change is real and to exclude precision errors of repeated measurements. In the case of RA, a 1-year observation period might not be long enough to draw any solid conclusion. Hence, a 3-year follow-up period, as with our study, seems more adequate to assess BMD changes and has been performed in several pivotal anti-osteoporosis medication studies [44, 45].

A strength of our study is that we measured and recorded many variables at baseline, including levels of 25(OH) Vitamin D intact parathyroid hormone (iPTH), mean DAS28-ESR and lifestyle, among others that could potentially influence BMD changes during the study period. In addition, most previous studies were single-arm studies without a control group or with a control group of patients without RA, which might not provide confirmative evidence regarding whether b/tsDMARD has a better bone loss protective effect than csDMARD. This was our rationale for enrolling an adequate control group by PSM. After PSM, the major contributing factors, such as age, gender, body weight and BMI were adjusted between the groups. This study design is a novel investigation model for researching the effect of DMARDs on BMD in patients with RA. Furthermore, we included participants who received AOT before enrolment or during the observation period. In this way, we were able to analyse the synergistic effect of b/tsDMARD and AOT on bone.

The current study has some limitations. We did not measure bone markers to support our observations. However, the results of previous studies on biologics in terms of bone marker changes were consistent with our results [8, 27, 46–48], showing an increase in bone formation markers and a decrease in bone resorption markers. In addition, bone markers are only a surrogate index of BMD changes and are subject to significant day-to-day variations, which is why we did not measure bone markers in this study. Fracture prevention is a difficult outcome of our study instead of BMD changes only.
However, data concerning the effects of b/tsDMARD on fracture risk are scarce and reveal conflicting results [49, 50]. Our data did not find a significantly lower new fracture rate in Group I than Group II (data not shown). In the future, studies must enrol more participants and have a longer follow-up to be able to elucidate whether b/tsDMARD therapy can reduce fracture risk compared with csDMARD therapy. In the current study, we enrolled participants who received either biologics or target therapy (JAK inhibitors). In these groups, we could not differentiate between the extent of bone loss protection effect.

Further studies are warranted to explore the specific influence of each biologic or target therapy on bone health and metabolism, and future research should focus on better profiling of patients with RA, targeting various therapeutic choices and more extended observation periods.

Conclusion

We conclude that long-term b/tsDMARDs therapy for patients with RA had a protective effect on bone loss at all sites measured. On the other hand, patients on conventional therapy experienced substantial bone density loss. Patients with RA who received AOT experienced a protective effect on bone loss, irrespective of b/tsDMARDs or csDMARDs therapy.

Acknowledgement

We are grateful for the support and instruction we have received from Taiwan Bone Muscle Joint Total Care Association (TBMJ).

Funding: This work was supported with grant CMRPG8F1111 from Chang Gung Memorial Hospital (https://www.cgmh.org.tw/), which sponsored the cost.
of data collecting, inputting and processing as well as the publication. The funder had no role in the study design, data analysis, decision to publish or manuscript preparation.

Disclosure statement: The authors have declared no conflicts of interest.

Supplementary data
Supplementary data are available at Rheumatology online.

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