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Impact of biologic disease-modifying antirheumatic drugs on fracture risk in patients with rheumatoid arthritis: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: This systematic review aimed to assess the impact of biologic disease-modifying antirheumatic drugs (bDMARDs) use on the risk of fracture in rheumatoid arthritis (RA) by conducting a pooled analysis of adjusted outcomes from individual studies.

MATERIALS AND METHODS: PubMed, Embase, and BioMed Central were searched up to 20th January 2021. Multivariable-adjusted odds ratios (OR) or matched estimates on the impact of bDMARDs on fracture risk were pooled.

RESULTS: Nine studies were included. We found no statistically significant difference in the risk of fractures in RA patients using bDMARDs vs. non-users. On sensitivity analysis, we found no change in the significance of the effect size on exclusion of any study. There was no statistically significant difference in fracture risk in studies only on tumor necrosis factor (TNF) inhibitors, as well as those including any bDMARDs. Pooled analysis of only three studies indicated a statistically significant reduction in vertebral fractures in bDMARD users vs. non-users.

CONCLUSIONS: Within the ambit of several limitations of our review, there seems to be no impact of bDMARDs on the fracture risk in RA patients. Further studies evaluating the type and duration of bDMARD therapy with meticulous adjustment of confounding factors are required to strengthen current evidence.

Key Words:
Osteoporosis, Fracture, Bone, Arthritis, Medications, Tumor necrosis factor inhibitors.

Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease characterized by pain and swelling of multiple joints in the body[1]. In addition to joint involvement, the chronic severe inflammation in RA results in many extra-articular manifestations and comorbidities, like cardiovascular diseases, depression, interstitial lung disease, infections, gastrointestinal diseases, and osteoporosis[2]. Indeed, several studies[3,4] in the literature have demonstrated an increased risk of osteoporosis and fractures in patients with RA as compared to the general population. Jin et al[3] in a meta-analysis of 25 studies have reported 1.5 times increased risk of fracture in RA patients. Scholars[5] have also indicated that fractures can lead to significant disability, poor quality of life, and increased mortality in RA patients.

Several different medications are prescribed for RA to manage pain and associated comorbidities. However, despite the high fracture burden in RA, limited research has been conducted on the impact of RA medications on bone loss and fracture risks[6,7]. One of the most commonly used drugs in RA patients to suppress inflammation and inhibit bone erosions are steroids. Contrastingly, steroids themselves can lead to secondary osteoporosis and increased fracture risk[8]. As expected, due to the widespread use of these drugs, some systematic reviews[8,9] in the recent past have focussed on the impact of steroid use on bone density and fracture risk in RA patients. Another group of drugs that have been developed due to our increased understanding of the systemic inflammatory process is biologic disease-modifying antirheumatic drugs (bDMARDs). These agents are developed from living organisms or their products

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and include drugs,like tumor necrosis factor (TNF) inhibitors (Adalimumab, Ertanacept, and Infliximab), Janus kinase (JAK) inhibitors (Baricitinib and Tofacitinib), etc[10]. The efficacy of these drugs is well established with a 2018 Cochrane review indicating that bDMARDs significantly improve RA symptoms, function, and remission rates in patients with prior treatment failure with methotrexate or conventional disease-modifying antirheumatic drugs (cDMARDs)[11]. Another area of research is the efficacy of bDMARDs on bone mineral density in RA patients. A recent study[12] has indicated that bDMARDs have a protective effect on bone loss as compared to cDMARDs. In this context, it would be interesting to know if the potent and specific anti-inflammatory action of bDMARDs also translates into a reduction of fracture risk in RA patients. To the best of our knowledge, no study to date has attempted to synthesize evidence on this subject. Therefore, our systematic review aimed to assess the impact of bDMARD use on the risk of fracture in RA patients by conducting a pooled analysis of adjusted outcomes from individual studies.

Materials and Methods

Inclusion Criteria

We followed the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-analyses) for the conduct of this review[13]. However, the protocol was not registered on any online database. Inclusion criteria were as follows: (1) All types of studies conducted on patients with RA. (2) Studies were to assess the impact of bDMARD use on fracture risk. (3) Studies were to report multi-variable matched or adjusted results of any type of fracture risk with bDMARD use *vs.* no use.

The following studies were excluded: (1) Studies reporting only crude outcome data. (2) Studies not reporting separate data for bDMARDs. (4) Studies published only as abstracts or unpublished papers. (3) Review articles and non-English language studies. If two or more studies were from the same data source, we included the one with the longest study period provided it fulfilled other criteria for inclusion.

Search Strategy

Two reviewers independently conducted the electronic search. With the help of a librarian, the databases of PubMed, Embase, and BioMed Central were searched to identify relevant publications. All databases were screened from inception to 20th January 2021. We used the combination of "rheumatoid arthritis" AND "fracture" for the literature search in all databases. Further keywords like "biological disease-modifying anti-rheumatic drugs" or "DMARDs" or names of specific bDMARDs were avoided as these would just create a sub-set of the primary search. Search results were deduplicated and then analyzed by the two reviewers independently. This was done first by reading the titles and abstracts and then by full-text analysis of relevant publications. All full-texts were reviewed based on the inclusion and exclusion criteria and the article satisfying all the criteria was finally selected for this review. Any disagreements were resolved by discussion. To avoid any missed studies, the bibliography of included studies was hand searched for any additional references.

Data Extraction and Risk of Bias Assessment

We prepared a data extraction form at the beginning of the review to extract relevant details from the studies. Details of the first author, publication year, study type, location, sample size, demographic details, users of bDMARDs, factors adjusted for multivariable analysis, and outcome data were extracted. The outcome of interest was fracture risk in patients prescribed with bDMARD as compared to non-users. Secondarily, we also aimed to assess the risk of specific types of fractures like vertebral, non-vertebral fractures with the use of bDMARDs.

The quality of included studies was assessed using the Newcastle-Ottawa scale[14]. Studies were awarded points for selection of study population, comparability, and outcomes. The maximum score which can be awarded is nine.

Statistical Analysis

All meta-analyses were performed using "Review Manager" (RevMan, version 5.3; Nordic Cochrane Centre [Cochrane Collaboration], Copenhagen, Denmark; 2014). We extracted multivariable-adjusted odds ratios (OR) or matched estimates of the outcomes along with the standard errors. Log transformed ratios were then pooled using the generic inverse function of the meta-analysis software. A random-effects model was preferred for the me-

ta-analysis. Sub-group analysis was performed based on the type of bDMARD used. Separate analysis for different types of fractures was performed only if at least three studies reported similar data.

The I^2 statistic was used to assess inter-study heterogeneity. Heterogeneity was classified as low with I^2 values of 25-50%, medium with values of 50-75% while I^2 value of more than 75% represented substantial heterogeneity. As less than 10 studies were included per meta-analysis, funnel plots were not used to assess publication bias. We also conducted a sensitivity analysis to assess the influence of each study on the overall effect size. Data of every study was sequentially excluded to recalculate the effect size and the results were presented in a tabular format.

Results

A total of 7916 articles were found following a literature search of the three databases (Figure 1). After electronically deduplicating the search results, 3112 unique records were available for further analysis. 3064 articles were excluded following the screening of their titles and abstracts. Of the 48 articles selected for full-text review, 37 were excluded with reasons. Finally, nine articles[15-23] were included in this systematic review and meta-analysis.

Characteristics of included studies are presented in detail in Table I. The included studies were published between 2012 to 2019. Four studies were conducted in North America, three in Asia, and two in Europe. The majority were retrospective cohort studies. The smallest sample size was

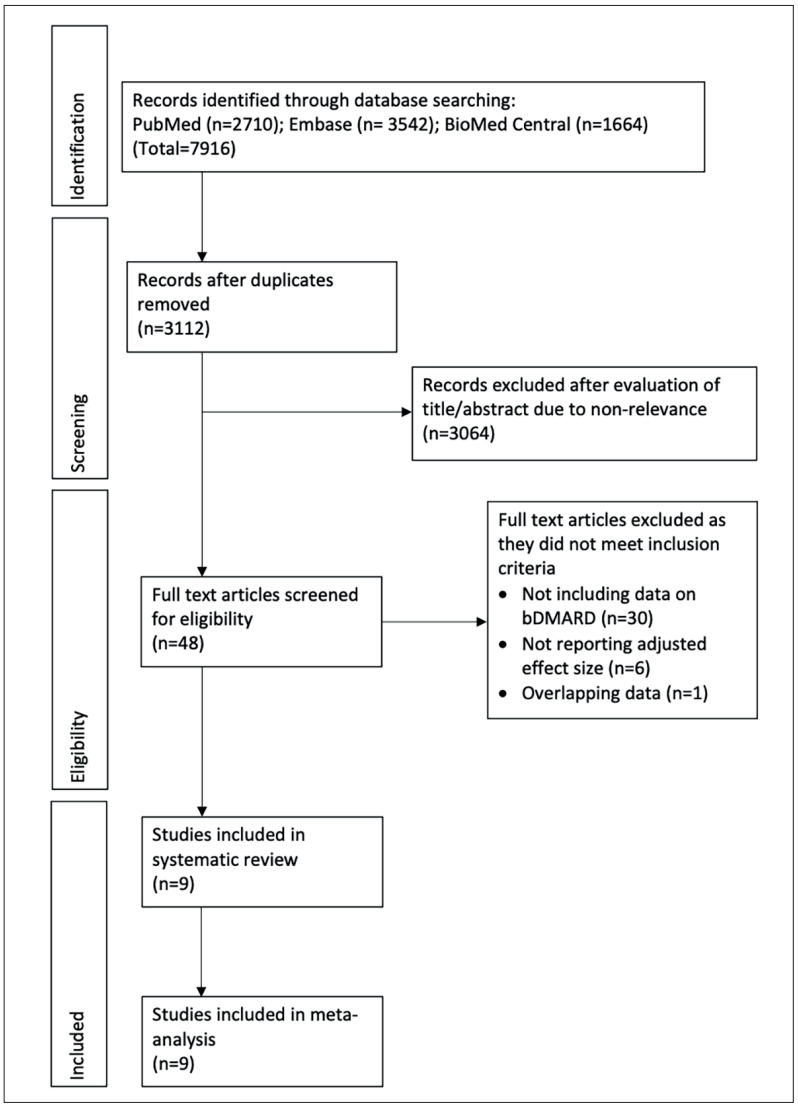

Figure 1. Study flow-chart.

Table I. Details of included studies.

Study	Study location	Study type	Sample size	Age (years)	Male gender (%)	Use of bDMARDs (%)	Fracture type studied	Cofounding factors adjusted	NOS score
Ozen 2019[22]	USA	Prospective cohort	11412	61.4 ± 10.8	20.1	51.2	All fractures, vertebral fracture, non-vertebral fracture	Age, sex, ethnicity, RA duration, education level, insurance, rural residency, smoking, influenza vaccination, comorbidity index, BMI, Health Assessment Questionnaire, pain and patient global scores, prior osteoporosis diagnosis, use of osteoporosis specific medications, exercise, mental component score of Short form-36, prior csDMARD and bDMARD counts, hospitalisation and calendar year	6
Hong 2019[21]	Taiwan	Retrospective cohort	1267	60.3 ± 10	36.9	3.7	Vertebral fracture	Gender, age, heart failure, hypertension, diabetes mellitus, vascular disease, hyperlipidemia, valvular heart disease, chronic obstructive pulmonary disease, and chronic kidney disease	6
Clynes 2019[20]	UK	Cross sectional	3849	57 [50-63]*	0	2.4	All fractures	Age, ethnicity, BMI, smoker status, and physical activity	4
Kim 2018[19]	Korea	Retrospective cohort	138240	54.2 ± 13.3	21.6	2.6	All fractures	Age, sex, payer type, type of institution, physician specialty, comorbidities (including hyperparathyroidism, hyperthyroidism, end stage renal disease, chronic pulmonary disease, and inflammatory bowel disease), oral steroid use, and medications related to rheumatoid arthritis and osteoporosis.	7
Jin 2017[23]	China	Retrospective cohort	13210	52.9 ± 13.1	29.4	8.3	All fractures	Age, sex, disease duration, anti-citrullinated protein antibody, disease activity score 28, steroid use, methotrexate use	7
Acurcio 2015[18]	Canada	Case-control	9769	76.2 ± 10.5	16.3	12.5	Non-vertebral fracture	Charlson index, osteoporosis, hospitalization, number medical visits and use of acetylsalicylic acid, antidepressants and hormone replacement therapy	7
Kawai 2013[17]	USA	Retrospective cohort	1840	58 [48-69]	13.8	50	All fractures, vertebral fracture, hip fracture	Demographic factors, comorbidities, surrogate markers of disease severity, previous fractures, diagnosis of osteoporosis, use of oral glucocorticoids, nonsteroidal anti-inflammatory drugs, narcotics, sedative hypnotics, muscle relaxants, antidepressants, antipsychotic agents, and use of drugs that affect bone metabolism [e.g., bisphosphonates, estrogens, thiazides]	7
Kim 2012[16]	Canada and USA	Retrospective cohort	13434	53.8 ± NR	24.7	43.6	All fracture; Hip, Humerus, Pelvis, Wrist fracture	Age, sex, baseline steroid use, diagnosis of osteoporosis, Alzheimer's dementia, Parkinson disease, prior fall, prior fracture, use of osteoporosisdrugs, anticonvulsants, benzodiazepines, opioids,selective serotonin reuptake inhibitors, and proton pump inhibitors, and Charlson Score.	7
Avouac 2012[15]	France	Cross sectional	139	61 ± 11	NR	40	All fractures	Age, osteoporosis, Vitamin D deficiency, Calcium supplementation	4

bDMARD, biological disease modifying antirheumatic drug; csDMARD, conventional synthetic disease modifying antirheumatic drug; BMI, body mass index; NOS, Newcastle-Ottawa scale. *Median [Interquartile range].

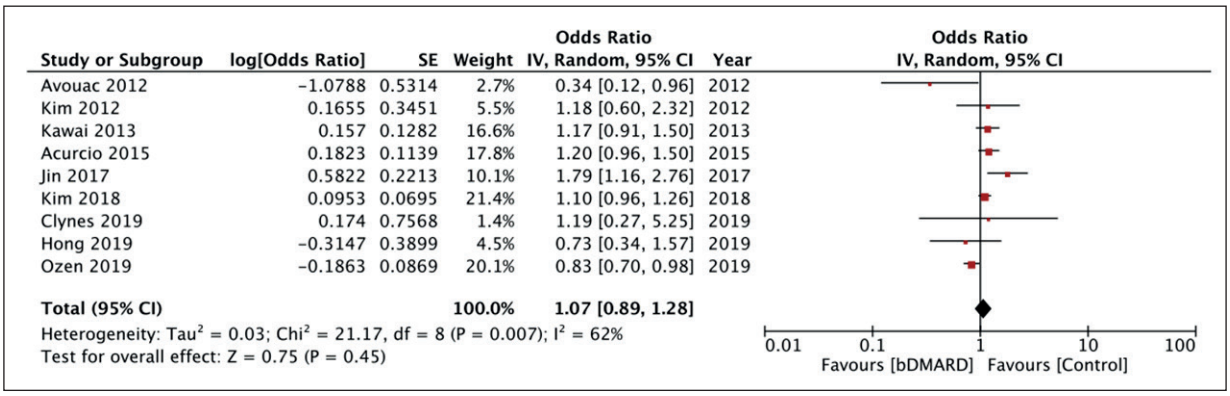

Figure 2. Meta-analysis of fracture risk in bDMARDS users *vs.* non-users.

139 patients while the largest sample size was 138,240 patients. There was a wide variation in the percentage of bDMARD users in the included studies ranging from 2.4% to 51.2%. Similar variation was noted for the factors adjusted for the multivariable analysis as well. While the majority of studies did not mention the type of bDMARD used, three studies conducted their analysis only on TNF inhibitors[17,19,21]. The Newcastle-Ottawa scale score for the included studies ranged from four to seven.

On meta-analysis of data from all nine studies including all fracture types, we found no statistically significant difference in the risk of fractures in RA patients using bDMARDs *vs.* non-users (OR 1.07 95% CI 0.89, 1.28 I^2=62% p=0.45) (Figure 2). On sensitivity analysis, we found no change in the significance of the effect size on the sequential exclusion of every included study (Table II). Since some studies included only TNF inhibitors, a sub-group analysis was conducted to pool them separately. However, we found no statistically significant difference in fracture risk in studies only on TNF inhibitors (OR 0.96 95% CI 0.75, 1.23 I^2=46% p=0.77), as well as those including any bDMARDs (OR 1.17 95% CI 0.91, 1.51 I^2=59% p=0.22) (Figure 3). Three studies reported the risk of vertebral fractures with bDMARDs. Pooled analysis indicated statistically significant reduction in vertebral fractures in bDMARD users *vs.* non-users (OR 0.71 95% CI 0.57, 1.28 I^2=0% p=0.002) (Figure 4).

Discussion

Fractures due to osteoporosis are the third most common cause of death in RA patients following pulmonary and cardiac diseases, and the second most common cause of disability following depression[24]. The high fracture burden in RA patients as compared to the general population has been identified in studies dating back to the 1980s[25]. However, despite advances in the therapeutic management of RA over several decades, the increased fracture risk persists in this cohort

Table II. Sensitivity analysis for the primary outcome.

Study excluded	Resultant effect size
Ozen 2019[22]	OR 1.15 95% CI 0.98, 1.36 I^2 = 37% p = 0.09
Hong 2019[21]	OR 1.09 95% CI 0.91, 1.31 I^2 = 65% p = 0.36
Clynes 2019[20]	OR 1.07 95% CI 0.89, 1.29 I^2 = 67% p = 0.48
Kim 2018[19]	OR 1.06 95% CI 0.83, 1.35 I^2 = 66% p =0.65
Jin 2017[23]	OR 1.02 95% CI 0.86, 1.20 I^2 = 54% p= 0.83
Acurcio 2015[18]	OR 1.04 95% CI 0.84, 1.29 I^2 = 64% p = 0.69
Kawai 2013[17]	OR 1.05 95% CI 0.85, 1.30 I^2 = 66% p = 0.64
Kim 2012[16]	OR 1.06 95% CI 0.88, 1.29 I^2 = 67% p = 0.52
Avouac 2012[15]	OR 1.10 95% CI 0.93, 1.30 I^2 = 58% p = 0.26

OR, Odds ratio; CI, confidence interval.

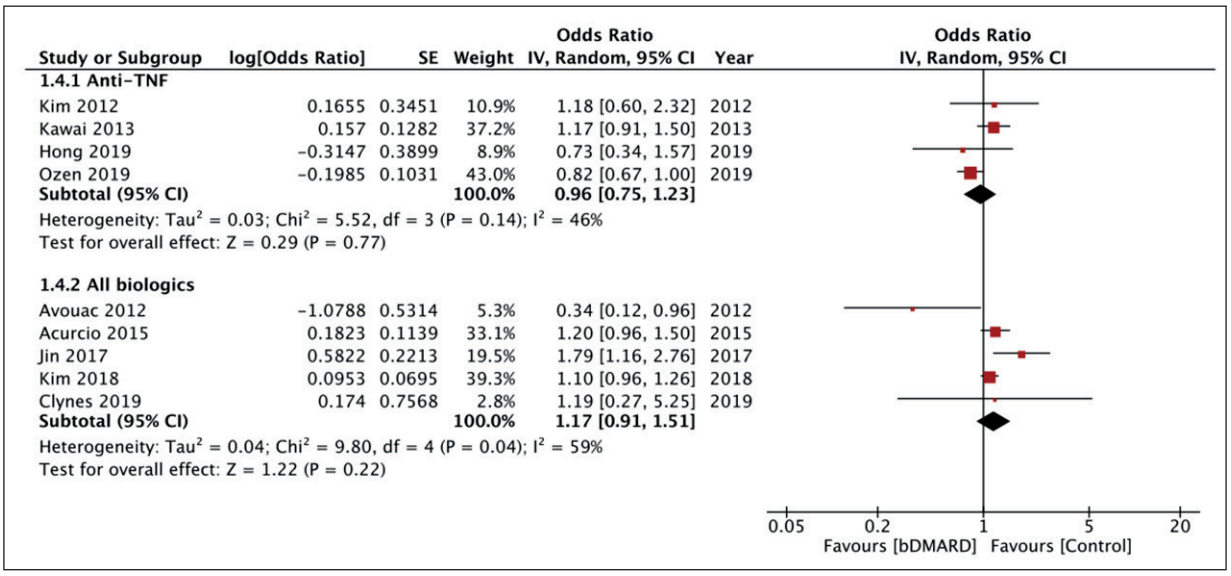

Figure 3. Meta-analysis of fracture risk in bDMARDS users *vs.* non-users based on the type of bDMARDS used.

of patients even in recent times[26]. Therefore, it is important to recognize modifiable risk factors for fractures in RA and importantly identify medications that can increase or decrease the risk of these fractures for better patient management.

The increased incidence of osteoporosis and fractures in RA is not only attributable to conventional risk factors, such as older age, female gender, and lower body mass index, but also several RA-related factors like extended use of steroids, disease activity, and inflammation[26,27]. Indeed, the role of proinflammatory cytokines, including TNF-α, interleukin-1, and interleukin-6 (IL-6) has been identified in bone loss associated with RA[28]. These cytokines are known to increase bone resorption by encouraging osteoclastic differentiation and increasing osteoclast activation[29]. Furthermore, these cytokines themselves may inhibit bone formation leading to an increased risk of osteoporosis[28,29]. Ding et al[30] have also demonstrated that circulating levels of inflammatory markers, like C-reactive protein, IL-6, and TNF- α are associated with bone loss and resorption in humans. Thus, as bone loss in RA is closely associated with inflammation, in theory, therapy with targeted anti-inflammatory agents like bDMARDs should augment bone health and reduce the risk of fractures in RA.

Our meta-analysis of nine studies using adjusted outcomes, however, failed to demonstrate any beneficial effect of bDMARDs on fracture risk in RA patients. The results were stable on sensitivity analysis and none of the included studies was found to have an undue influence on the effect size. Furthermore, on a detailed analysis of the forest plot, one can note that the majority of the included studies found no statistically significant difference in fracture risk between bDMARD users *vs.* non-users. We attempted to explore the inter-study heterogeneity by conducting a subgroup analysis based on the type of bDMARD. Due to the limited number of studies available, we could

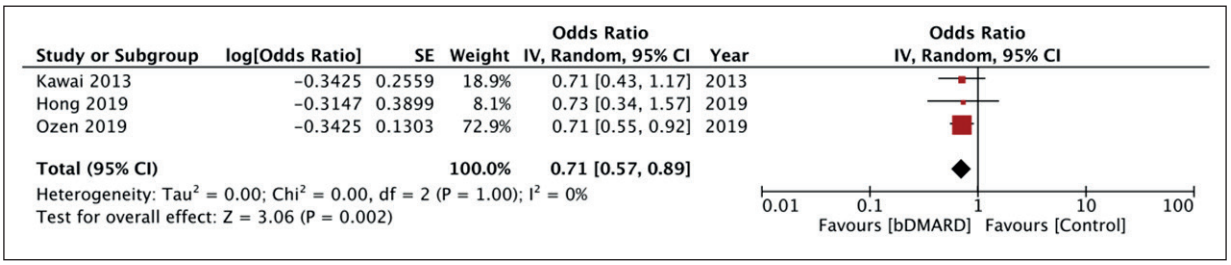

Figure 4. Meta-analysis of vertebral fracture risk in bDMARDS users *vs.* non-users.

separate the studies into only two groups: TNF inhibitors and all biologics. Results of this subgroup analysis also indicated no difference in the risk of fracture between the two groups.

Our results are in contradiction with studies[6,31] reporting the beneficial effects of bDMARDs on bone health using bone turnover markers. Several studies[6,32,33] with a limited sample size have indicated that treatment with bDMARDs improves bone mineral density in RA patients. Zerbini et al[6] in a recent detailed review of 28 studies have reported that treatment with bDMARDs, like TNF inhibitors, IL-6 blocking agents, rituximab, and abatacept is associated with a reduction in bone loss. However, the efficacy of bDMARDs in reducing bone loss in RA is not unambiguous. While the beneficial effect of bDMARDs is mostly demonstrated in retrospective cohort studies, evidence from randomized controlled trials (RCTs) suggests otherwise. Siu et al[34] in a meta-analysis of five RCTs comparing TNF inhibitors with non-bDMARDs reported significantly reduced hand bone loss but no improvement in the spine or hip bone mineral density with bDMARDs. It is postulated that the anti-inflammatory effect of antirheumatic drugs is centered around active joints where they improve periarticular osteopenia, and this may explain the lack of improvement in bone health at the hip or spine[34]. Our results could therefore be a corollary to this theory. A second explanation for the non-significant results could be related to the prescription pattern of bDMARDs in RA. Guidelines formulated by the European League Against Rheumatism (EULAR) recommend methotrexate and glucocorticoids as the first line of treatment in RA with bDMARDs to be used only if primary therapy fails[35]. In some countries bDMARDs are not covered in the health insurance policies and, due to their high costs, they are prescribed to patients only with higher disease activity, severe joint damage, and poor responses to conventional therapy[23]. Thus, patients on bDMARDs could have a higher baseline fracture risk owing to the increased disease severity which may have nullified the stronger anti-inflammatory action of bDMARDs.

Our meta-analysis demonstrated a significantly reduced risk of vertebral fractures in bDMARD users *vs.* non-users. However, this result should be interpreted with caution as only three studies were available for this analysis. Furthermore, the results were highly influenced by the single study of Ozen et al[22] which demonstrated a significantly reduced risk of vertebral fractures with TNF inhibitors but not with other bDMARDs. The remaining two studies of Hong et al[21] and Kawai et al[17] did not find any significant difference in vertebral fractures between bDMARD users vs non-users. Owing to the non-significant results of our primary outcome, we believe further studies are necessary to derive stronger conclusions on the effect of bDMARDs on the risk of vertebral fractures.

Limitations

Our review has several limitations. Firstly, as none of the studies were RCTs there would have been evident selection bias in the prescription of bDMARDs. Despite using only adjusted outcomes for our analysis the effect of residual confounding due to other unmeasured risk factors cannot be completely negated. Furthermore, there was wide variation in the included studies in the variables adjusted for the analysis. A few of the included studies missed important confounders, like steroid use which is a known risk factor of osteoporosis and fractures in RA. Secondly, the studies also differed in the sample size and the percentage of bDMARD users. In three studies[19-21], the use of bDMARDs was less than 5%. Such low numbers would have reduced the power to detect significant associations in these studies. While the majority of studies reported the risk of all fractures, two studies reported the risk of only vertebral[21] on non-vertebral fractures[18]. Thirdly, the incidence of fractures was extracted from medical records in the majority of studies. Inadequate radiographic screening for fractures could have underestimated fracture risk. Lastly, the specific type and duration of bDMARD use were not described in the included studies. Therefore, it is currently not known if there are inter-drug variations amongst bDMARDs for fracture risk and if the duration of treatment influences outcomes.

Despite these limitations, our study has some novelties. While optimal evidence on the impact of bDMARDs on fracture risk in RA can only be obtained by rigorously conducted RCTs, conducting such a trial is difficult due to ethical and funding issues, need for long-term follow-up, and comparing several bDMARDs, to study an uncommon outcome like the risk of fracture. In this context, our study is the first to present the best available evidence in the literature to date. A detailed literature search was conducted using broad keywords to include the maximum

available studies. We pooled data of only adjusted outcomes to avoid confounding as much as possible. Appropriate sensitivity and sub-group analysis were conducted to assess inter-study heterogeneity.

Conclusions

To sum up, within the ambit of several limitations of our review, there seems to be no impact of bDMARDs on fracture risk in RA patients. Further studies evaluating the type and duration of bDMARD therapy with meticulous adjustment of confounding factors are required to strengthen current evidence. However, the best evidence can be obtained only from RCTs.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' Contribution

FS designed the project; HL and MW were involved in data collection and data analysis; FS prepared the manuscript; CC edited the manuscript; all authors read and approved the final manuscript.

References

1) Pisetsky DS. Advances in the treatment of rheumatoid arthritis: costs and challenges. N C Med J 2017; 78: 337-340.
2) Otón T, Carmona L. The epidemiology of established rheumatoid arthritis. Best Pract Res Clin Rheumatol 2019; 33.
3) Jin S, Hsieh E, Peng L, Yu C, Wang Y, Wu C, Wang Q, Li M, Zeng X. Incidence of fractures among patients with rheumatoid arthritis: a systematic review and meta-analysis. Osteoporos Int 2018; 29: 1263-1275.
4) Xue AL, Wu SY, Jiang L, Feng AM, Guo HF, Zhao P. Bone fracture risk in patients with rheumatoid arthritis. Medicine (United States) 2017; 96: e6983.
5) Lin YC, Li YH, Chang CH, Hu CC, Chen DW, Hsieh PH, Lee MS, Ueng SW, Chang Y. Rheumatoid arthritis patients with hip fracture: a nationwide study. Osteoporos Int 2015; 26: 811-817.
6) Zerbini CAF, Clark P, Mendez-Sanchez L, Pereira RMR, Messina OD, Uña CR, Adachi JD, Lems WF, Cooper C, Lane NE; IOF Chronic Inflammation and Bone Structure (CIBS) Working Group. Biologic therapies and bone loss in rheumatoid arthritis. Osteoporosis Int 2017; 28: 429-446.
7) Raterman HG, Bultink IE, Lems WF. Osteoporosis in patients with rheumatoid arthritis: an update in epidemiology, pathogenesis, and fracture prevention. Expert Opin Pharmacother 2020; 21: 1-13.
8) Blavnsfeldt ABG, de Thurah A, Thomsen MD, Tarp S, Langdahl B, Hauge EM. The effect of glucocorticoids on bone mineral density in patients with rheumatoid arthritis: a systematic review and meta-analysis of randomized, controlled trials. Bone 2018; 114: 172-180.
9) Wang Y, Zhao R, Gu Z, Dong C, Guo G, Li L. Effects of glucocorticoids on osteoporosis in rheumatoid arthritis: a systematic review and meta-analysis. Osteoporos Int 2020; 31: 1401-1409.
10) Choy EH. Effect of biologics and targeted synthetic disease-modifying anti-rheumatic drugs on fatigue in rheumatoid arthritis. Rheumatology (United Kingdom) 2019; 58 Suppl 5: V51-V55.
11) Singh JA, Hossain A, Tanjong Ghogomu E, Mudano AS, Tugwell P, Wells GA. Biologic or tofacitinib monotherapy for rheumatoid arthritis in people with traditional disease-modifying anti-rheumatic drug (DMARD) failure: a Cochrane Systematic Review and network meta-analysis (NMA). Cochrane Database Syst Rev 2016; 11: CD012437.
12) Chen JF, Hsu CY, Yu SF, Ko CH, Chiu WC, Lai HM, Chen YC, Su YJ, Cheng TT. The impact of long-term biologics/target therapy on bone mineral density in rheumatoid arthritis: a propensity score-matched analysis. Rheumatology (Oxford) 2020; 59: 2471-2480.
13) Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. PLoS Med 2009; 6: e1000097.
14) Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed 30 Oct 2020.
15) Avouac J, Koumakis E, Toth E, Meunier M, Maury E, Kahan A, Cormier C, Allanore Y. Increased risk of osteoporosis and fracture in women with systemic sclerosis: a comparative study with rheumatoid arthritis. Arthritis Care Res (Hoboken) 2012; 64: 1871-1878.
16) Kim SY, Schneeweiss S, Liu J, Solomon DH. Effects of disease-modifying antirheumatic drugs on nonvertebral fracture risk in rheumatoid arthritis: a population-based cohort study. J Bone Miner Res 2012; 27: 789-796.
17) Kawai VK, Grijalva CG, Arbogast PG, Curtis JR, Solomon DH, Delzell E, Chen L, Ouellet-Hellstrom

R, Herrinton L, Liu L, Mitchell EF Jr, Stein CM, Griffin MR. Initiation of tumor necrosis factor α antagonists and risk of fractures in patients with selected rheumatic and autoimmune diseases. Arthritis Care Res (Hoboken) 2013; 65: 1085-1094.

18) Acurcio FA, Moura CS, Bernatsky S, Bessette L, Rahme E. Opioid use and risk of nonvertebral fractures in adults with rheumatoid arthritis: a nested case-control study using administrative databases. Arthritis Rheumatol 2016; 68: 83-91.

19) Kim D, Cho SK, Park B, Jang EJ, Bae SC, Sung YK. Glucocorticoids are associated with an increased risk for vertebral fracture in patients with rheumatoid arthritis. J Rheumatol 2018; 45: 612-620.

20) Clynes MA, Jameson K, Prieto-Alhambra D, Harvey NC, Cooper C, Dennison EM. Impact of rheumatoid arthritis and its management on falls, fracture and bone mineral density in UK biobank. Front Endocrinol (Lausanne) 2019; 10: 817.

21) Hong WJ, Chen W, Yeo KJ, Huang PH, Chen DY, Lan JL. Increased risk of osteoporotic vertebral fracture in rheumatoid arthritis patients with new-onset cardiovascular diseases: a retrospective nationwide cohort study in Taiwan. Osteoporos Int 2019; 30: 1617-1625.

22) Liou YS, Lin TK, Chen HY, Jong GP. Medications associated with fracture risk in patients with rheumatoid arthritis. Ann Rheum Dis 2019: annrheumdis-2019-216262.

23) Jin S, Li M, Fang Y, Li Q, Liu J, Duan X, Liu Y, Wu R, Shi X, Wang Y, Jiang Z, Wang Y, Yu C, Wang Q, Tian X, Zhao Y, Zeng X; CREDIT Co-authors. Chinese Registry of rheumatoid arthritis (CREDIT): II. prevalence and risk factors of major comorbidities in Chinese patients with rheumatoid arthritis. Arthritis Res Ther 2017; 19: 251.

24) Michaud K, Wolfe F. Comorbidities in rheumatoid arthritis. Best Pract Res Clin Rheumatol 2007; 21: 885-906.

25) Hooyman JR, Melton LJ 3rd, Nelson AM, O'Fallon WM, Riggs BL. Fractures after rheumatoid arthritis. A population-based study. Arthritis Rheum 1984; 27: 1353-1361.

26) Guañabens N, Olmos JM, Hernández JL, Cerdà D, Hidalgo Calleja C, Martinez López JA, Arboleya L, Aguilar Del Rey FJ, Martinez Pardo S, Ros Vilamajó I, Suris Armangué X, Grados D, Beltrán Audera C, Suero-Rosario E, Gómez Gracia I, Salmoral Chamizo A, Martín-Esteve I, Florez H, Naranjo A, Castañeda S, Ojeda Bruno S, García Carazo S, García Vadillo A, López Vives L, Martínez-Ferrer À, Borrell Paños H, Aguado Acín P, Castellanos-Moreira R, Tebé C, Gómez-Vaquero C; OsteoResSer Working Group of the Spanish Society of Rheumatology. Vertebral fractures are increased in rheumatoid arthritis despite recent therapeutic advances: a case-control study. Osteoporos Int 2021. doi: 10.1007/s00198-021-05824-7. Epub ahead of print.

27) Tong JJ, Xu SQ, Zong HX, Pan MJ, Teng YZ, Xu JH. Prevalence and risk factors associated with vertebral osteoporotic fractures in patients with rheumatoid arthritis. Clin Rheumatol 2020; 39: 357-364.

28) Shim JH, Stavre Z, Gravallese EM. Bone loss in rheumatoid arthritis: basic mechanisms and clinical implications. Calcif Tissue Int 2018; 102: 533-546.

29) Karmakar S, Kay J, Gravallese EM. Bone damage in rheumatoid arthritis: mechanistic insights and approaches to prevention. Rheum Dis Clin North Am 2010; 36: 385-404.

30) Ding C, Parameswaran V, Udayan R, Burgess J, Jones G. Circulating levels of inflammatory markers predict change in bone mineral density and resorption in older adults: a longitudinal study. J Clin Endocrinol Metab 2008; 93: 1952-1958.

31) Tawaratsumida H, Setoguchi T, Arishima Y, Ohtsubo H, Akimoto M, Ishidou Y, Nagano S, Taketomi E, Sunahara N, Komiya S. Risk factors for bone loss in patients with rheumatoid arthritis treated with biologic disease-modifying anti-rheumatic drugs. BMC Res Notes 2017; 10: 765.

32) Marotte H, Pallot-Prades B, Grange L, Gaudin P, Alexandre C, Miossec P. A 1-year case-control study in patients with rheumatoid arthritis indicates prevention of loss of bone mineral density in both responders and nonresponders to infliximab. Arthritis Res Ther 2007; 9: R61.

33) Seriolo B, Paolino S, Sulli A, Ferretti V, Cutolo M. Bone metabolism changes during anti-TNF-alpha therapy in patients with active rheumatoid arthritis. Ann N Y Acad Sci 2006; 1069: 420-427.

34) Siu S, Haraoui B, Bissonnette R, Bessette L, Roubille C, Richer V, Starnino T, McCourt C, McFarlane A, Fleming P, Kraft J, Lynde C, Gulliver W, Keeling S, Dutz J, Pope JE. Meta-analysis of tumor necrosis factor inhibitors and glucocorticoids on bone density in rheumatoid arthritis and ankylosing spondylitis trials. Arthritis Care Res (Hoboken) 2015; 67: 754-764.

35) Smolen JS, Landewé RBM, Bijlsma JWJ, Burmester GR, Dougados M, Kerschbaumer A, McInnes IB, Sepriano A, van Vollenhoven RF, de Wit M, Aletaha D, Aringer M, Askling J, Balsa A, Boers M, den Broeder AA, Buch MH, Buttgereit F, Caporali R, Cardiel MH, De Cock D, Codreanu C, Cutolo M, Edwards CJ, van Eijk-Hustings Y, Emery P, Finckh A, Gossec L, Gottenberg JE, Hetland ML, Huizinga TWJ, Koloumas M, Li Z, Mariette X, Müller-Ladner U, Mysler EF, da Silva JAP, Poór G, Pope JE, Rubbert-Roth A, Ruyssen-Witrand A, Saag KG, Strangfeld A, Takeuchi T, Voshaar M, Westhovens R, van der Heijde D. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis 2020; 79: 685-699.