Biological disease-modifying antirheumatic drugs and osteoporotic fracture risk in patients with rheumatoid arthritis

CLINICAL RESEARCH STUDY

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Biological Disease-Modifying Antirheumatic Drugs and Osteoporotic Fracture Risk in Patients with Rheumatoid Arthritis: A Danish Cohort Study

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ABSTRACT

OBJECTIVES: Clinical trials have shown a beneficial effect from biological disease-modifying antirheumatic drugs (bDMARDs) on hand or axial bone loss in patients with rheumatoid arthritis; however, it is unclear if this translates to a reduced fracture risk. We investigated the effect of bDMARDs on osteoporotic fracture risk compared to no biological treatment in rheumatoid arthritis.

METHODS: A cohort of patients with rheumatoid arthritis aged 18+ from DANBIO was linked to population-based health registries in Denmark (2006-2016). Adopting a prevalent new-user design, we matched bDMARD users to bDMARD-naïve patients using time-conditional propensity scores. The risk of incident osteoporotic fractures (including hip, vertebrae, humerus, and forearm) was estimated among the matched patients by Cox proportional hazards models.

RESULTS: Out of 24,678 patients with rheumatoid arthritis, 4265 bDMARD users were matched to the same number of bDMARD-naïve patients (mean age 56.2 years, 74% female). During follow-up, 229 osteoporotic fractures occurred among bDMARD users and 205 fractures among bDMARD-naïve patients (incidence rates 12.1 and 13.0 per 1000 person-years, respectively). The use of bDMARDs was not associated with a reduced risk of osteoporotic fractures among patients with rheumatoid arthritis (hazard ratio 0.97, 95% confidence interval 0.78-1.20), compared with no biological treatment. The risk estimates were similar for all osteoporotic fracture sites.

CONCLUSION: We found no independent beneficial effect from using bDMARDs on reducing the risk of osteoporotic fractures in patients with rheumatoid arthritis.

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INTRODUCTION

Rheumatoid arthritis is the most common autoimmune rheumatic disease with a predisposition to osteoporosis and osteoporotic fractures.[1-3] The key players in this increased susceptibility are underlying disease process, reduced physical activity, low body mass index (BMI), and pharmacological treatment of the disease, especially with oral glucocorticoids.[3,4] Biological disease-modifying antirheumatic drugs (bDMARDs) along with conventional synthetic DMARDs (csDMARDs) are the cornerstone of rheumatoid arthritis pharmacotherapy, where bDMARDs are potent suppressors of the chronic inflammatory process of the disease. However, their effect on osteoporotic fracture risk is less clear.

CLINICAL SIGNIFICANCE

- Using biological disease-modifying antirheumatic drugs had no independent beneficial effect on reducing osteoporotic fracture risk in patients with rheumatoid arthritis.
- There was no effect modification by sex or disease activity of rheumatoid arthritis at baseline.
- Biological disease-modifying antirheumatic drugs do not increase fracture risk, in contrast to other anti-inflammatory drugs used in rheumatoid arthritis, such as glucocorticoids.

Certain pathophysiological processes during the course of rheumatoid arthritis can result in alterations of bone remodeling in favor of more bone resorption and, ultimately, higher rates of osteoporotic fractures. Pro-inflammatory systemic and local cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, IL-17, macrophage colony-stimulating factor, and the imbalance of ratio between receptor activator of nuclear factor-κB ligand (RANKL) and osteoprotegerin (OPG) have a pivotal role in stimulating osteoclasts and increasing bone resorption.[5] Therefore, it seems plausible that bDMARDs can reverse bone loss or protect against osteoporotic fractures in rheumatoid arthritis. Clinical trials have shown inconsistent results for a protective effect of TNF inhibitors (infliximab or adalimumab) on bone health in rheumatoid arthritis by preventing hand or generalized bone mineral density loss at the hip or spine, although the number of included patients was small.[6-9] Additionally, although a few studies have failed to show a beneficial effect of bDMARDs in reducing fracture rates,[10-13] data from observational studies is limited. The lack of data from clinical trials, paucity of observational studies, and the high disease burden of osteoporotic fractures pose an unmet need for more data on the role of bDMARDs in fracture risk in rheumatoid arthritis. Thus, we investigated the effect of bDMARDs on osteoporotic fracture risk compared with no biological treatment in patients with rheumatoid arthritis.

METHODS

Data Source

We conducted a population-based cohort study using data from nationwide administrative health registers linked to the DANBIO (full name: DANBIO – The Danish Rheumatologic Database). DANBIO is a nationwide clinical register in Denmark used in routine care of patients with rheumatic diseases including rheumatoid arthritis since 2000.[14] It includes information on confirmed diagnoses by rheumatologists and treatment series with bDMARDs, csDMARDs, and glucocorticoids, in addition to patient demographics and disease status markers. Data on vital status for the Danish population have been collected since 1968 in the Civil Registration System, which included approximately 5.4 million individuals in 2006 and 5.7 million in 2016.[15] All hospitalization records have been registered in the Danish National Patient Registry (DNPR) since 1977; also starting from 1995 it incorporates all outpatient diagnoses and services using the *International Classification of Diseases, 10th Revision* (ICD-10).[16,17] Moreover, since 1995 all drug prescriptions dispensed in Denmark are collected in the Register of Medicinal Product Statistics, as a prescription database.[18] The validity of rheumatoid arthritis diagnosis in DANBIO and registration of fracture records in DNPR have been previously verified.[19,20] The unique 10-digit civil registry number allocated to each Danish citizen was used to link all aforementioned registries to produce a complete medical and drug history for each patient.

Study Population and Design

All patients older than 18 years of age with rheumatoid arthritis and with a first recorded visit in DANBIO between January 1, 2006, and December 31, 2016, were included (Figure 1).[21] The date of first visit recorded in DANBIO determined the *cohort baseline*. We used a prevalent new-user design to compare the first use of a bDMARD with no biological treatment in a cohort of prevalent and new users of csDMARDs.[22] This design was selected because the majority of bDMARD users have prior use of csDMARDs, based on the current European Alliance of Associations for Rheumatology (EULAR) guidelines for rheumatoid arthritis management.[23] Thus, an incident new-user design was not suitable.[24]

Exposure and Outcome

The primary exposure of interest was use of any bDMARD with an indication for rheumatoid arthritis in Denmark, including infliximab, adalimumab, etanercept, certolizumab, golimumab, abatacept, tocilizumab, rituximab, and anakinra. The csDMARDs used in pharmacotherapy of rheumatoid arthritis in Denmark consisted of methotrexate, hydroxychloroquine, sulfasalazine, and leflunomide. The

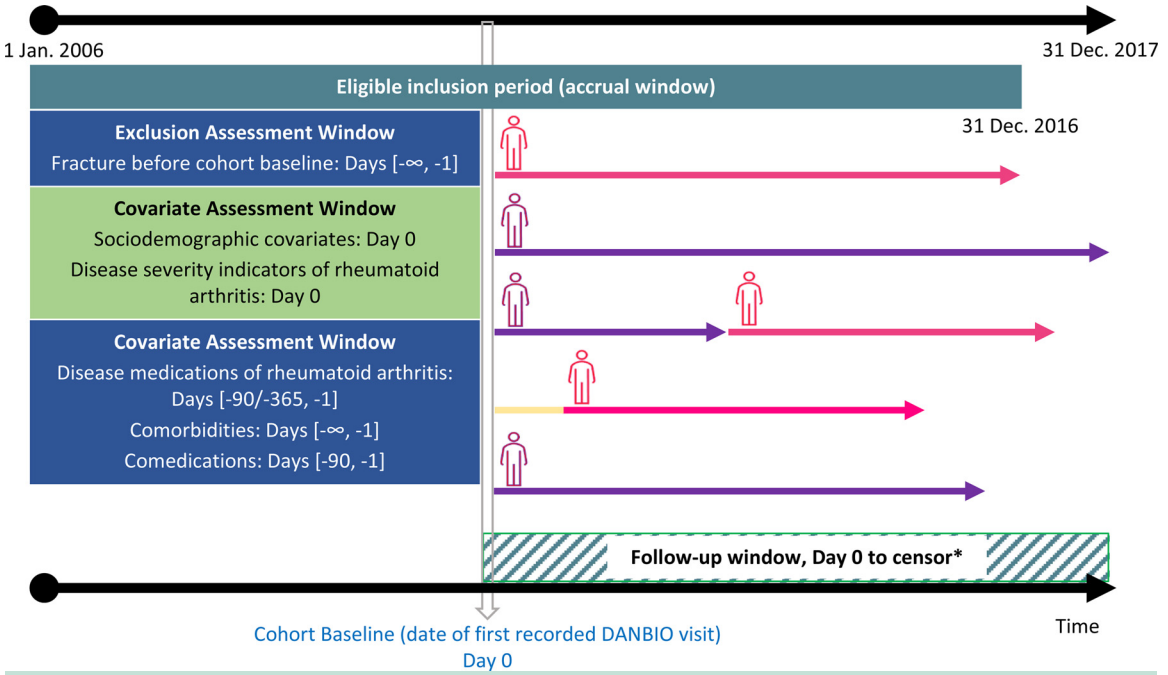

Figure 1 Study design. A blue window shows data extraction from the Danish National Patient Registry, and a green window shows data extraction from the DANBIO. A pink caricature and follow-up line represents a bDMARD user, and a purple one represents a bDMARD-naïve patient. The yellow line in the exemplar graph shows days since cohort entry for a bDMARD user. In case of those bDMARD users with an index date later than the cohort baseline, all covariates and exclusion criteria have been assessed at the index date. For a detailed explanation of sociodemographic covariates, disease severity indicators of rheumatoid arthritis, disease medications of rheumatoid arthritis, comorbidities, and comedications please refer to Supplementary Table S1, available online. bDMARD = biological disease-modifying antirheumatic drug; DANBIO = DANBIO — The Danish Rheumatologic Database. *Earliest of: outcome of interest (fracture), death, emigration, end of 2017, >365-days without DANBIO visit, starting of bDMARD among the comparison group, or recorded stop date of bDMARD.

starting date of a bDMARD on or after cohort baseline defined the *index date* for bDMARD users. For the comparison group (ie, bDMARD-naïve patients), the date of cohort baseline defined the *index date*. The bDMARD users were permitted to have prior exposure to a csDMARD (Figure 1).

The main outcome was occurrence of the first incident osteoporotic fracture in patients after the index date, extracted from the DNPR using the Danish version of ICD-10. These included hip (S72.0-S72.2), clinically symptomatic vertebral (S12, S22.0, S22.1, S32.0, T08), humerus (S42.2-S42.4), and forearm (S52).[25] All patients were followed from the index date until the outcome of interest, or death, emigration, end of study period (December 31, 2017), >1 year after the last recorded visit in DANBIO, switching from csDMARD to bDMARD (identified as start date of bDMARD), or stop date of bDMARD. For all analyses, patients had a minimum of 1-year follow-up (last inclusion date December 31, 2016 with follow-up until December 31, 2017). Patients with a history of fracture ever before the index date were excluded.

Matching and Covariate Selection

We used a propensity-score (PS) matching model to minimize confounding by indication.[26] The time-conditional PS estimated the probability of receiving a given treatment (bDMARD vs no bDMARD) using multivariable logistic regression including all covariates mentioned. Each bDMARD user was then matched 1:1 to a patient with no biological use with the most similar time-conditional PS within a caliper distance of 0.2 standard deviations of the logit of the PS, using greedy matching.[27] Overlap in PSs was checked by plotting the distribution of PSs for both exposure groups separately, before and after matching. Patients falling outside this region were unmatched and excluded from further analysis. By design, bDMARD-naïve patients could initiate a bDMARD at a later time point and be "reused" in the analysis as a new bDMARD patient, where they would be matched to a bDMARD-naïve patient with a similar PS.[22] A set of sociodemographic covariates, severity indicators of rheumatoid arthritis, comorbidities, and comedications, as established risk factors of osteoporotic fractures, were included in the PS calculations (Supplementary Table S1, available online).[3,26,28] When variables had <10% missing, multiple imputation was used, and when missing was >10%, those variables were excluded from the model.

Statistical Analysis

Descriptive statistics were used to summarize the baseline characteristics of patients before and after matching.

Differences between bDMARD users and bDMARD-naïve patients were assessed using standardized mean differences, where a threshold of <0.1 indicates well-balanced characteristics. Cox proportional hazards models were used to estimate the risk of osteoporotic fractures between the 2 PS-matched pairs of rheumatoid arthritis patients, which means those exposed to any bDMARD (considering all various bDMARDs together) and the comparison group (ie, bDMARD-naïve patients). Separate analyses were conducted for the individual osteoporotic fracture sites. Time-to-event curves were constructed to show the risk of osteoporotic fractures over time in both exposure groups.

Additionally, we stratified these analyses by sex and disease activity at baseline. The stratification by disease activity was according to the Disease Activity Score in 28 joints with C-reactive protein (DAS28-CRP), with 2 strata of remission to low (DAS28-CRP score <3.2) and moderate to high disease activity (DAS28-CRP score ≥3.2). For both stratifications, PSs were recalculated within each sex or DAS28 stratum and then PS matching was performed using the same approach as the primary analysis. In a sensitivity analysis, we repeated the primary analysis by only excluding individuals with a fracture in 1-year before the index date. Data were analyzed using R version 4.0.3.

RESULTS

The study population comprised of 24,678 patients with rheumatoid arthritis between 2006 and 2016, where more than one-fifth (N = 5214) were bDMARD users (Figure 2). The bDMARD users had a more severe disease assessed by higher DAS28-CRP scores (4.3 vs 3.7) and longer duration of rheumatoid arthritis (8.3 vs 5.9 years) than the comparison group (Table 1). They also had used more oral glucocorticoids (33% vs 16%) in the year prior to the index date. Around 79% of bDMARD users were prevalent users of csDMARDs in the 90 d before the index date, whereas only 63% of the comparison group were taking csDMARDs in a similar time window.

We matched 4265 bDMARD users to the same number of bDMARD-naïve patients based on their PS in the main analysis. Following PS matching, the covariates were well-balanced between the 2 cohorts (Table 1, Supplementary Figure, available online). The mean follow-up time for bDMARD users after matching was 4.4 years, whereas that of bDMARD-naïve patients was 3.7 years. The information on body mass index, smoking status, and alcohol use were not reported and, hence, not considered in the PSs due to the high number of missing values.

During follow-up, 229 osteoporotic fractures occurred among the bDMARD users with an incidence rate of 12.1 per 1000 person-years, whereas 205 osteoporotic fractures occurred among the comparison group with an incidence rate of 13.0 per 1000 person-years (Table 2). The use of bDMARDs was not associated with a reduced risk of osteoporotic fractures among patients with rheumatoid arthritis compared with no biological use (hazard ratio [HR] 0.97, 95% confidence interval [CI] 0.78-1.20). No individual osteoporotic fracture site observed a significant reduction in risk with bDMARD use versus no biological use Figure 3. depicts the time-to-event curves for both exposure groups since the index date, with no apparent detachment during the entire follow-up period (>10 years).

Table 3 shows the stratified analyses by sex. Use of bDMARDs was not associated with a reduced risk of osteoporotic fractures in both women (HR 0.90, 95% CI 0.68-1.20) and men (HR 0.78, 95% CI 0.44-1.41) compared with no treatment with biologicals. Similarly, there was no reduced risk with bDMARD use for any individual fracture site among both sexes.

Similarly, we did not observe an effect modification by disease activity at baseline (Supplementary Table S2, available online). There was no reduced risk in any of the osteoporotic fracture sites among patients with remission to low disease activity and those who had a moderately to highly active disease at baseline, when comparing bDMARD use to no biological use.

When only excluding patients with a fracture in 1-year prior, we observed numerically lower risk estimates in bDMARD users for osteoporotic fractures and for those of the hip and clinical vertebral compared to the main analysis in Table 2 (Supplementary Table S3, available online). But still, there was no statistically significantly reduced risk with bDMARD use versus the comparator group for none of the fracture sites.

DISCUSSION

Our results showed that bDMARDs did not reduce osteoporotic fracture risk in patients with rheumatoid arthritis compared with no biological use. Similarly, none of the individual osteoporotic fractures had a lower risk with bDMARDs. Our stratified analyses revealed that there was no effect modification by sex or rheumatoid arthritis disease activity at baseline.

Our results of a nonbeneficial effect of bDMARDs on fracture risk in rheumatoid arthritis are mainly in line with the few observational studies in this topic,[10-13] despite the differences in design and characteristics. These included the use of different databases (administrative or claims databases compared to a nationwide clinical database in our study), difference in follow-up (1-2 years vs >4 years mean follow-up), and not considering vertebral fracture in the studies by Kim et al[11] and Roussy et al.[13] The only negative association between TNF inhibitor use and overall risk of all factures (and not for those of the hip and spine) comes from an observational study with a short follow-up time (<1 year), and no appropriate consideration of timing of exposure and outcome, thus prone to several biases.[10]

The hypothesized beneficial effect of bDMARDs on fracture risk is based on the effect of biological drugs on bone health.[5] However, this is also not consistent in the literature. There are some clinical trials and observational studies that have shown a gain, stability, or prevention of

Table 1 Baseline Characteristics of Study Population at Index Date, Stratified by bDMARD Use for the Whole Cohort and for the Propensity-Score Matched Patients

	Before Matching					After Matching				
	bDMARD-treated patient (N = 5214)		bDMARD-naïve patients (N = 19,464)		SMD	bDMARD-treated patients (N = 4265)		bDMARD-naïve patients (N = 4265)		SMD
	N	%	N	%		N	%	N	%	
Mean duration of follow-up (y), SD	4.5	3.1	3.7	2.7		4.4	3.1	3.7	3.0	
Mean age (y), SD*	55.7	12.9	60.2	14.0	−0.345	56.2	13.1	56.2	12.8	−0.002
Number of females	3907	74.9	13,448	69.1	0.135	3164	74.2	3177	74.5	−0.007
Educational level*										
Low	1642	31.5	7098	36.5	−0.107	1361	31.9	1344	31.5	0.009
Medium	3177	60.9	11,131	57.2	0.077	2589	60.7	2589	60.7	0.000
High	224	4.3	677	3.5	0.04	178	4.2	178	4.2	0.000
Unknown	171	3.3	558	2.9	0.023	137	3.2	154	3.6	−0.022
Year of cohort entry*										
2006	402	7.7	690	3.5	0.156	304	7.1	309	7.2	−0.004
2007	575	11.0	2408	12.4	−0.043	514	12.1	534	12.5	−0.015
2008	534	10.2	1022	5.3	0.165	423	9.9	431	10.1	−0.006
2009	582	11.2	1448	7.4	0.118	458	10.7	460	10.8	−0.001
2010	564	10.8	1967	10.1	0.023	470	11.0	483	11.3	−0.010
2011	454	8.7	2042	10.5	−0.063	372	8.7	354	8.3	0.015
2012	430	8.2	2032	10.4	−0.080	349	8.2	351	8.2	−0.002
2013	454	8.7	2193	11.3	−0.091	392	9.2	366	8.6	0.022
2014	429	8.2	2160	11.1	−0.104	352	8.3	355	8.3	−0.003
2015	382	7.3	1835	9.4	−0.081	313	7.3	312	7.3	0.001
2016	408	7.8	1667	8.6	−0.028	318	7.5	310	7.3	0.007
Disease severity indicators*										
Mean DAS28-CRP,† SD	4.3	1.1	3.7	1.4	0.534	4.2	1.2	4.2	1.3	0.014
Mean HAQ score,† SD	1.0	0.7	0.8	0.7	0.258	1	0.7	1	0.7	0.006
Mean disease duration (y), SD	8.3	9.1	5.9	9.3	0.266	7.9	8.7	8	11.6	−0.015
Mean CRP, SD	9.0	3.5	6.7	3.6	0.159	8.5	3.5	8.4	3.6	0.010
Seropositivity‡	4013	77.0	13,333	68.5	0.201	3210	75.3	3166	74.2	0.025
Mean VAS-patient, SD	53	24.1	45.5	28.3	0.313	52.5	24.3	52.5	26.9	−0.002
Swollen joints count, median, and IQR	3	1-6	2	0-5	0.233	3	1-6	3	1-6	0.018
Tender joints count, median, and IQR	5	2-9	3	0-7	0.219	4	2-9	4	2-9	−0.010
Disease Medications										
csDMARDs (90 d before)	4137	79.3	12,208	62.7	0.411	3291	77.2	3265	76.6	0.015
Methotrexate	3521	67.5	10,388	53.4	0.302	2795	65.5	2763	64.8	0.016
Hydroxychloroquine	1011	19.4	1144	5.9		808	18.9	369	8.7	
Sulfasalazine	1526	29.3	2969	15.3		1205	28.3	912	21.4	
Leflunomide	22	0.4	45	0.2		17	0.4	15	0.4	
Oral GCs (≥2 prescriptions)§	1707	32.7	3124	16.1	0.356	1208	28.3	1149	26.9	0.029
GC injections and infusions§	2804	53.8	5922	30.4	0.468	2114	49.6	2050	48.1	0.030
Infliximab	1357	26.0	0	0		1119	26.2	0	0	
Adalimumab	1097	21.0	0	0		882	20.7	0	0	
Etanercept	1166	22.4	0	0		958	22.5	0	0	
Certolizumab	701	13.4	0	0		590	13.8	0	0	
Golimumab	152	2.9	0	0		128	3.0	0	0	
Abatacept	280	5.4	0	0		216	5.1	0	0	
Tocilizumab	236	4.5	0	0		190	4.5	0	0	
Rituximab	222	4.3	0	0		179	4.2	0	0	
Anakinra	≤3	—	0	0		≤3	—	0	0	
History of Comorbidities										
Asthma	214	4.1	796	4.1	0.001	180	4.2	183	4.3	−0.004
COPD	291	5.6	1035	5.3	0.011	236	5.5	231	5.4	0.005
Ischemic heart disease	404	7.7	1773	9.1	−0.051	330	7.7	347	8.1	−0.015
Cerebrovascular disease	156	3	722	3.7	−0.042	128	3.0	121	2.8	0.010
Chronic heart failure	95	1.8	460	2.4	−0.040	84	2.0	98	2.3	−0.025
Peripheral vascular disease	45	0.9	280	1.4	−0.062	41	1.0	34	0.8	0.018
Gastroesophageal reflux disease	171	3.3	645	3.3	−0.002	139	3.3	150	3.5	−0.014
Peptic ulcer disease	86	1.6	348	1.8	−0.011	75	1.8	72	1.7	0.006
Celiac disease	7	0.1	19	0.1		6	0.1	5	0.1	0.006
Inflammatory bowel disease	92	1.8	251	1.3	0.036	75	1.8	69	1.6	0.011
Thyroid disorders (hypo- and hyperthyroidism)	426	8.2	1410	7.2	0.034	332	7.8	330	7.7	0.002
Diabetes mellitus (both types 1 and 2)	291	5.6	1104	5.7	−0.004	236	5.5	218	5.1	0.018
Osteomalacia	12	0.2	27	0.1	0.019	9	0.2	8	0.2	0.005
Osteoporosis	398	7.6	1262	6.5	0.043	306	7.2	305	7.2	0.001
Chronic renal failure	34	0.7	117	0.6	0.006	26	0.6	26	0.6	0.000
Dementia	20	0.4	81	0.4	−0.005	18	0.4	20	0.5	−0.008
Malignant neoplasms (excluding nonmelanoma skin cancers)	224	4.3	1422	7.3	−0.148	191	4.5	196	4.6	−0.006
Comedication use (90 d before)										
Antihypertensives	1943	37.3	8140	41.8	−0.094	1602	37.6	1560	36.6	0.020
Statins	508	9.7	2694	13.8	−0.138	437	10.2	446	10.5	−0.007

Table 1 (*Continued*)

	Before Matching					After Matching				
	bDMARD-treated patient (N = 5214)		bDMARD-naïve patients (N = 19,464)		SMD	bDMARD-treated patients (N = 4265)		bDMARD-naïve patients (N = 4265)		SMD
	N	%	N	%		N	%	N	%	
Anticoagulants	538	10.3	2854	14.7	−0.143	457	10.7	452	10.6	0.004
Bisphosphonates	577	11.1	1480	7.6	0.110	419	9.8	412	9.7	0.005
Hormone replacement therapy	284	5.4	1051	5.4	0.002	230	5.4	251	5.9	−0.022
Intravenous anti-osteoporotic drugs§	8	0.2	15	0.1	0.020	4	0.1	5	0.1	−0.006
Nonsteroidal anti-inflammatory drugs	1843	35.3	7176	36.9	−0.032	1533	35.9	1479	34.7	0.026
Paracetamol	2300	44.1	7176	36.9	0.146	1804	42.3	1790	42.0	0.007
Opioids	1037	19.9	3350	17.2	0.067	838	19.6	817	19.2	0.012
Anticonvulsants	103	2.0	462	2.4	−0.029	92	2.2	90	2.1	0.003
Hypnotics/Anxiolytics	431	8.3	1493	7.7	0.022	357	8.4	358	8.4	−0.001
Antidepressants	420	8.1	1540	7.9	0.005	346	8.1	346	8.1	0.000
Antipsychotics	64	1.2	251	1.3	−0.006	54	1.3	39	0.9	0.032

bDMARD = biological disease-modifying antirheumatic drug; COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; csDMARD = conventional synthetic disease-modifying antirheumatic drug; DAS28 = Disease Activity Score in 28 joints; GCs = glucocorticoids; HAQ = health assessment questionnaire; IgM = immunoglobulin; IQR = interquartile range; SD = standard deviation; SMD = standardized mean difference; VAS-patient = Visual Analogue Scale-patient's global.

The SMD values are only reported for those covariates that were used in the propensity scores calculations.

*At index date (see Figure 1).

†No missing values before and after matching for both patient groups due to imputation.

‡This means either a positive IgM-rheumatoid factor, a positive anticitrullinated peptides antibody, or both.

§In the 1-year before index date (see Figure 1).

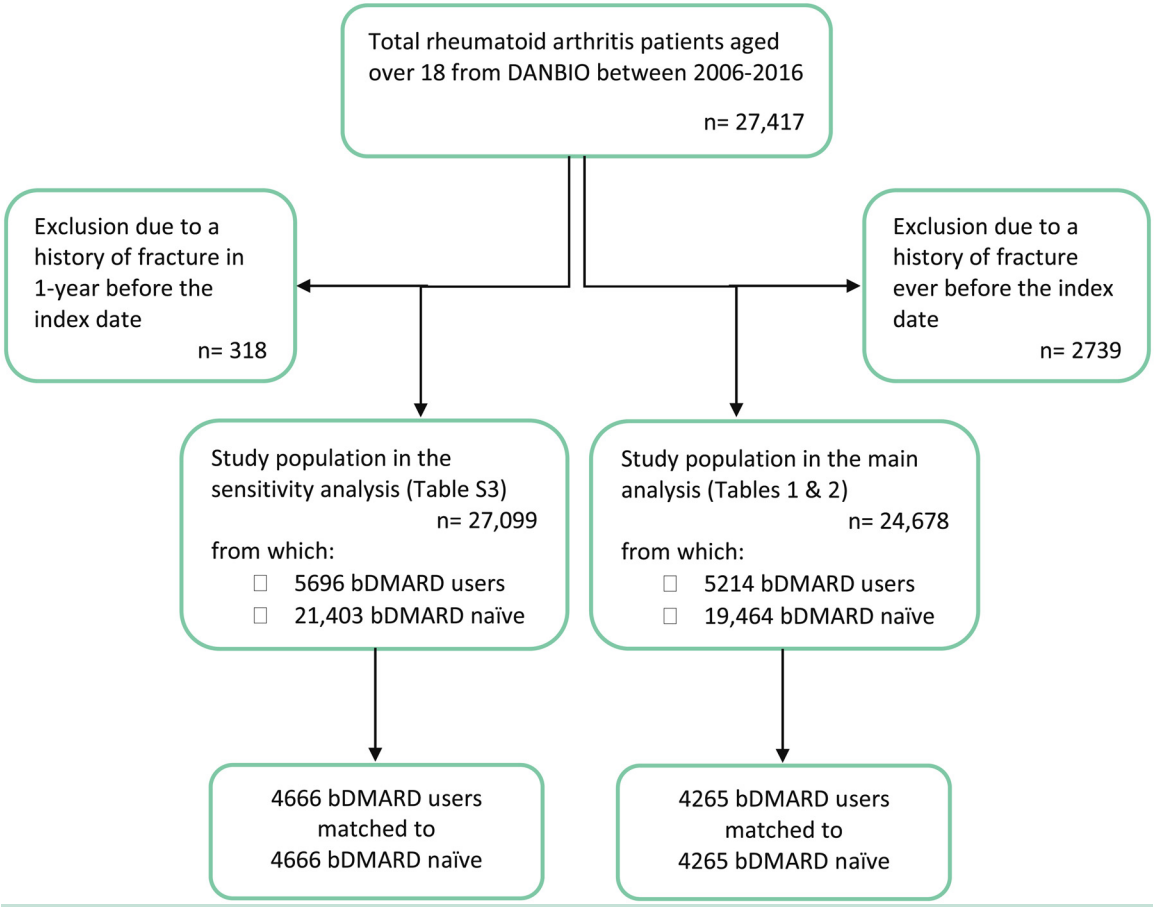

Figure 2 Flowchart on establishment of patient population. bDMARD = biological disease-modifying antirheumatic drug; DANBIO = DANBIO – The Danish Rheumatologic Database.

Table 2 Osteoporotic Fracture Risk Associated with bDMARD Use in Patients with Rheumatoid Arthritis Compared with No Biological Use in Propensity-Score Matched Analysis, Stratified by Fracture Type

By fracture type	Patient group	Number of fractures	Py	IR per 1000 py	Hazard ratio (95% CI)
Osteoporotic fractures	bDMARD naïve	205	15,722.0	13.0	Reference
	bDMARD user	229	18,954.0	12.1	0.97 (0.78-1.20)
Hip fracture	bDMARD naïve	52	16,234.7	3.2	Reference
	bDMARD user	52	19,530.2	2.7	0.92 (0.57-1.49)
Clinical vertebral fracture	bDMARD naïve	17	16,333.3	1.0	Reference
	bDMARD user	23	19,616.4	1.2	1.32 (0.65-2.68)
Humerus fracture	bDMARD naïve	53	16,175.3	3.3	Reference
	bDMARD user	70	19,440.1	3.6	1.14 (0.74-1.75)
Forearm fracture	bDMARD naïve	103	16,027.6	6.4	Reference
	bDMARD user	108	19,364.8	5.6	0.85 (0.64-1.13)

bDMARD = biological disease-modifying antirheumatic drug; CI = confidence interval; IR = incidence rate; py = person-years.

loss in bone mineral density at the hip or spine after using infliximab, adalimumab, or tocilizumab in patients with rheumatoid arthritis.[7-9,29-33] In contrast, other studies have shown a protective effect of biological agents on hand bone loss and not on the axial bone health.[6,34,35] Most of these studies were open-label uncontrolled single-arm trials, but there were a few with an active comparator group, such as methotrexate.[6,8,34]

To date, the only known mechanism for an effect of bDMARDs on bone health is through the inflammatory pathway.[5] The arrest in generalized bone loss after starting infliximab in rheumatoid arthritis was accompanied by a decreasing RANKL/OPG ratio, a proxy of bone resorption.[32] Dickkopf-1 protein correlates to rheumatoid arthritis disease severity and is a key inhibitor of the Wingless protein cascade, which per se is an important stimulator of osteoblast maturation and activity.[5] Decreased serum levels of dickkopf-1 was observed after treatment with tocilizumab, infliximab, and anakinra in patients with rheumatoid arthritis along with an arrest in bone loss at the hip and lumbar spine.[30,36] Our exposure drugs consisted of various biological agents targeting different parts of the

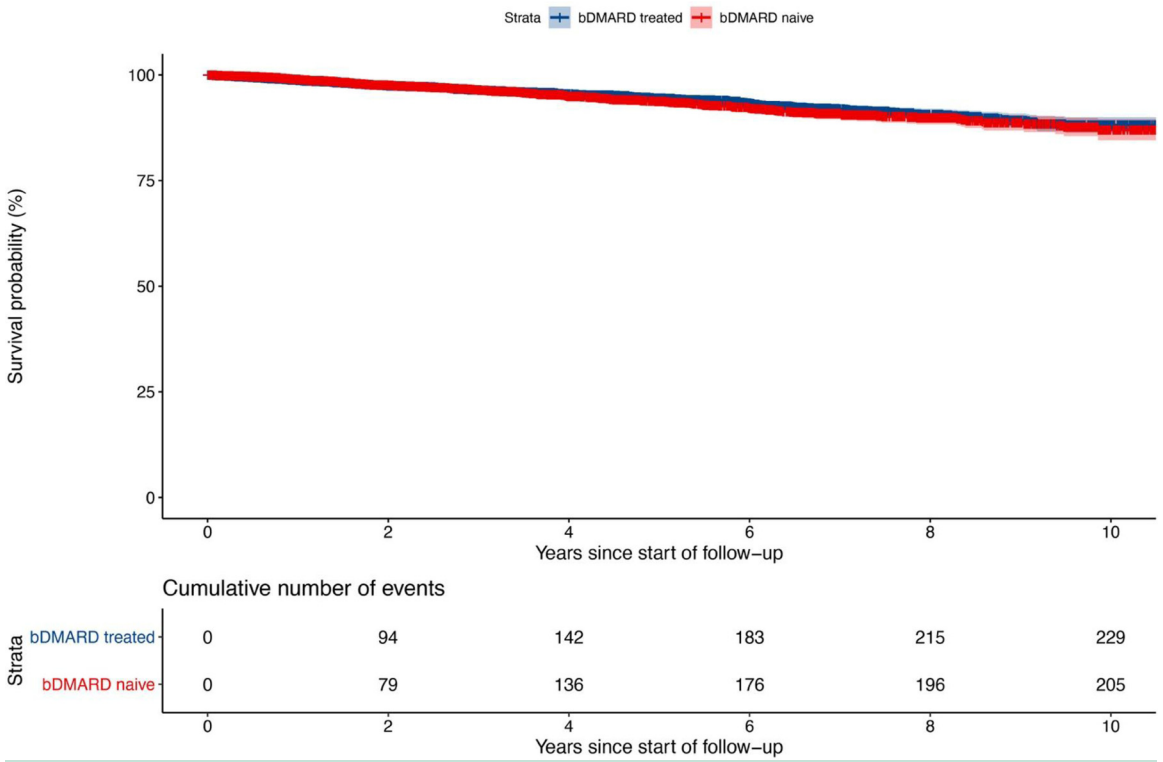

Figure 3 Time-to-event curves showing the osteoporotic fracture events over time for rheumatoid arthritis patients who used biological DMARDs, and those who were not using any biologicals, hence bDMARD-naïve. bDMARD = biological disease-modifying antirheumatic drug.

Table 3 Osteoporotic Fracture Risk Associated with bDMARD use in Rheumatoid Arthritis Patients Compared with No Biological Use in Propensity-Score Matched Analysis, Stratified by Sex and Fracture Type

	Patient group	Number of fractures	Py	IR per 1000 py	Hazard Ratio (95% CI)
Among Women					
Osteoporotic fractures	bDMARD naïve	203	11,613.0	17.5	Reference
	bDMARD user	196	14,055.0	13.9	0.90 (0.68-1.20)
Hip fracture	bDMARD naïve	58	12,088.8	4.8	Reference
	bDMARD user	43	14,550.9	3.0	0.81 (0.52-1.27)
Clinical vertebral fracture	bDMARD naïve	16	12,218.8	1.3	Reference
	bDMARD user	19	14,629.7	1.3	1.23 (0.57-2.65)
Humerus fracture	bDMARD naïve	58	12,054.3	4.8	Reference
	bDMARD user	66	14,461.8	4.6	1.07 (0.69-1.64)
Forearm fracture	bDMARD naïve	94	11,946.1	7.9	Reference
	bDMARD user	90	14,426.0	6.2	0.85 (0.59-1.21)
Among Men					
Osteoporotic fractures	bDMARD naïve	32	3790.0	8.4	Reference
	bDMARD user	27	4752.0	5.7	0.78 (0.44-1.41)
Hip fracture	bDMARD naïve	9	3853.8	2.3	Reference
	bDMARD user	4	4820.2	0.8	0.82 (0.12-5.73)
Clinical vertebral fracture	bDMARD naïve	7	3873.2	1.8	Reference
	bDMARD user	4	4829.9	0.8	0.71 (0.05-9.24)
Humerus fracture	bDMARD naïve	5	3869.6	1.3	Reference
	bDMARD user	6	4816.0	1.2	0.67 (0.15-3.09)
Forearm fracture	bDMARD naïve	12	3847.0	3.1	Reference
	bDMARD user	14	4792.7	2.9	0.96 (0.33-2.77)

bDMARD = biological disease-modifying antirheumatic drug; CI = confidence interval; IR = incidence rate; py = person-years.

inflammatory cycle (ie, TNF-α, IL-1, IL-6, CD20, or CD80/86). We attempted to emulate the randomization of a randomized controlled trial design by PS matching and balancing the disease activity at baseline. However, we did not further adjust for changes in disease activity during follow-up, and information on bone markers during follow-up was not available. But because we used real-world data from a specialty clinical database, we can expect optimal control of disease activity in bDMARD-naïve patients who were treated with a "treat-to-target" strategy by rheumatologists with csDMARDs or glucocorticoids. This means, control of disease activity in both comparison groups resulted in comparable beneficial effects on bone health and fracture risk, and hence, no reduction in fracture risk among bDMARD users versus no biological treatment. This is an important difference between observational studies (including ours) that reported a neutral effect of bDMARDs on fracture risk,[11-13] and those single-arm clinical trials, which reported a beneficial effect on bone mineral density in a quasi-experimental before-after design.[7,9,29-32]

An important alternative interpretation of our study was that bDMARDs do not increase the fracture risk, in contrary to many other anti-inflammatory or other drugs used in the management of rheumatoid arthritis. Previous studies have shown that oral glucorticoids,[3,37-39] some csDMARDs such as methotrexate,[11,40] proton pump inhibitors,[38] opioids,[41] and selective serotonin reuptake inhibitors,[41] were associated with an increased risk of osteoporotic fractures in patients with rheumatoid arthritis. The good safety profile and strong anti-inflammatory effects had indeed a major role in making bDMARDs the second-line therapy for rheumatoid arthritis in the recent EULAR guidelines.[23]

Our study had several strengths. Using comprehensive nationwide registries linked to DANBIO not only enabled us to include almost all patients with rheumatoid arthritis in Denmark but also provided the ability to adjust for disease severity indicators (such as DAS28, and CRP). We also benefited from a longer follow-up time and inclusion of clinical vertebral fracture, compared to previous studies in this topic. We used an advanced study design (ie, prevalent new-user design) that enabled us to include both incident and prevalent users of csDMARDs as the first-line treatment in rheumatoid arthritis and to adjust for the potential imbalance between our exposure groups by means of time-conditional PS matching.

Limitations

Despite the strengths, this study was not free from limitations. First, although we PS-matched patients, time-lag bias might have occurred due to different follow-up times for our comparison groups after matching (4.4 vs 3.7 years).[42] A longer follow-up period among bDMARD users could mean a more advanced disease state of rheumatoid arthritis and hence an increased fracture risk due to the inflammatory process of the disease in comparison with the control group. This increased fracture risk might have masked the hypothetical beneficial effect of bDMARDs. Additionally, we did not account for treatment adherence with the orally taken csDMARDs, where 26% of patients with rheumatoid

arthritis were estimated to be nonadherent to methotrexate during the first months of therapy.[43] This might result in misclassification of exposure by shifting the risk estimate toward or away from the null,[44] supposing a hypothetical protective effect from bDMARDs and a detrimental effect from csDMARDs (especially methotrexate) on fracture risk.[11,40] Furthermore, not including body mass index, smoking status, and alcohol use in the PS model due to a large number of missing values might have caused some unmeasured confounding to our results.

CONCLUSION

In conclusion, bDMARDs had no independent beneficial effect on reducing the risk of osteoporotic fractures in patients with rheumatoid arthritis. Our results are in line with previous observational studies on bDMARDs and fracture risk in rheumatoid arthritis and also consenting with beneficial effect of biological drugs on bone mineral density identified in single-arm before-after trials. Future studies are needed to further elucidate any beneficial relationship among bDMARDs, bone mineral density, and osteoporotic fracture risk in patients with rheumatoid arthritis.

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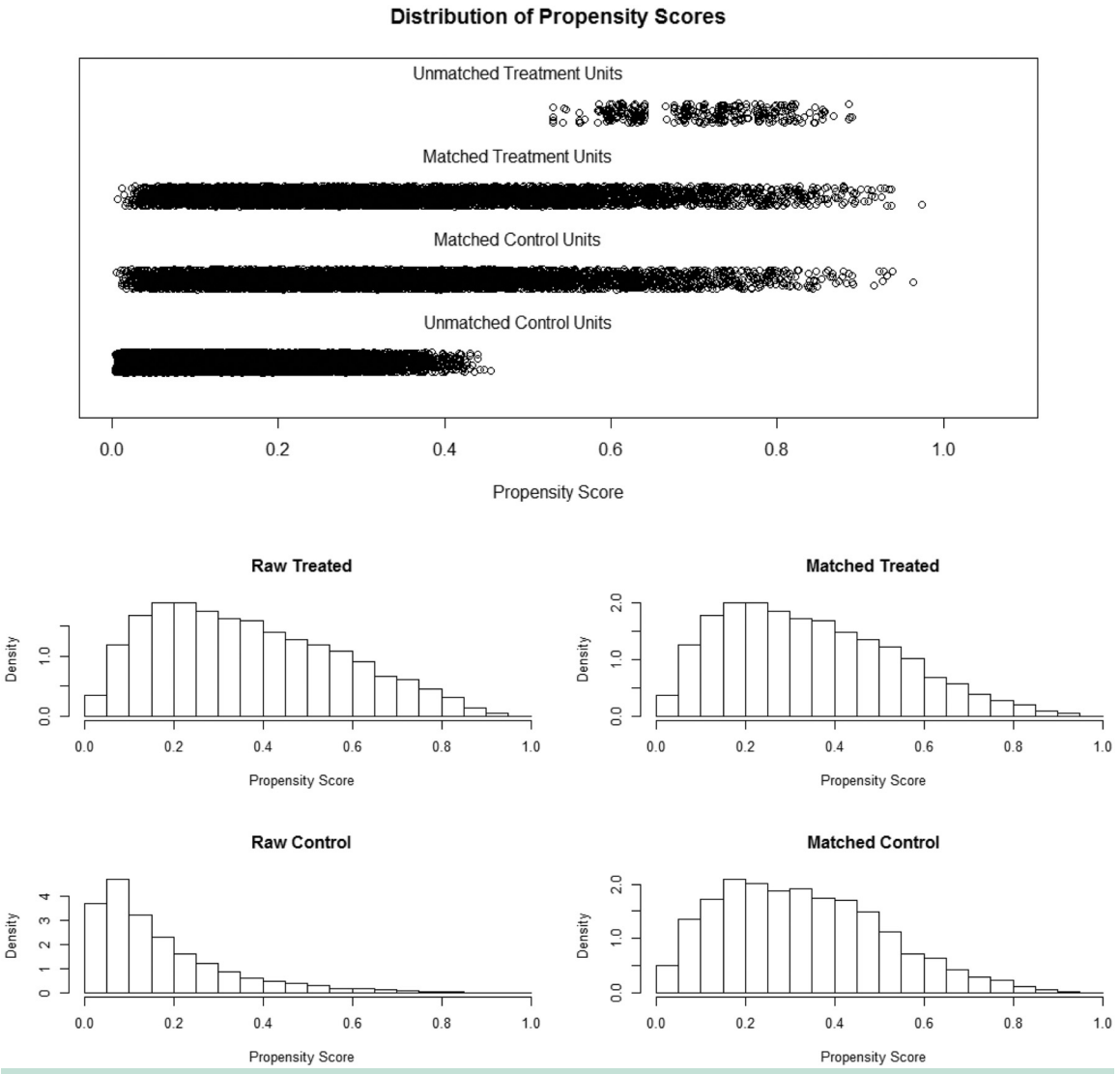
SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjmed.2022.01.017.

Supplementary Table S1 Variables Used in the Propensity-Score Matching

Sociodemographic covariates (at index date)	Age	Disease severity indicators of rheumatoid arthritis (at index date)	DAS28-CRP
	Sex (categorical)		Disease duration (in years)
	Body mass index		CRP
	Smoking status		Rheumatoid factor
	Alcohol use		Anticitrullinated peptides antibody
	Educational level (categorical)		Heath Assessment Questionnaire score
	Income quintile		Visual Analog Scale (pain, fatigue, patient's global)
	Cohort entry year (categorical)		Swollen joints count
	Days since cohort entry (baseline; continuous)		Tender joints count
Disease medications of rheumatoid arthritis	csDMARDs (in past 90 d)		
	2 or more oral glucocorticoids (in the past year)		
	Glucocorticoid injections (in past year, yes/no)		
Comedications (90 d before index date)	Antihypertensives	Comorbidities (ever before index date)	Asthma
	Statins		COPD
	Anticoagulants		Myocardial infarction
	Bisphosphonates		Stroke
	Intravenous anti-osteoporotic drugs (past year)		Chronic heart failure
			Peripheral vascular disease
	Hormone replacement therapy		Peptic ulcer disease
	Nonsteroidal anti-inflammatory drugs		Gastroesophageal reflux disease
			Celiac disease
	Paracetamol		Inflammatory bowel disease
	Opioids (including tramadol)		Diabetes mellitus
	Anticonvulsants		Thyroid disorders
	Anxiolytics		Hypopituitarism
	Antidepressants		Osteomalacia
	Antipsychotics		Osteoporosis
			Bilateral oophorectomy/orchidectomy
			Chronic renal failure
			Dementia
			Anorexia nervosa
			Malignancies
			Falls
			Organ transplantation

csDMARDs = conventional synthetic disease-modifying antirheumatic drugs; COPD: chronic obstructive pulmonary disease; CRP = C-reactive protein; DAS28-CRP = Disease Activity Score in 28 joints with C-reactive protein.



Supplementary Figure Histograms of distributions of propensity scores per exposure groups before and after matching. Treated (or treatment unit) shows patients who received bDMARDs and control (or control unit) signifies those who did not receive bDMARDs. bDMARD = biological disease-modifying antirheumatic drug.

Supplementary Table S2 Evaluating Osteoporotic Fracture Risk Associated with bDMARD Use in Rheumatoid Arthritis Patients Compared with No Biological Use in Propensity-Score Matched Analysis, Stratified by Disease Activity Level and Fracture Type

	Patient group	Number of fractures	Py	IR per 1000 py	Hazard ratio (95% CI)
Remission-Low (DAS28-CRP score <3.2)					
Osteoporotic fractures	bDMARD naïve	42	3154.0	13.3	Reference
	bDMARD user	39	3335.0	11.7	0.89 (0.50-1.58)
Hip fracture	bDMARD naïve	13	3250.8	4.0	Reference
	bDMARD user	7	3441.9	2.0	0.69 (0.16-2.95)
Clinical vertebral fracture	bDMARD naïve	4	3289.9	1.2	Reference
	bDMARD user	≤3	NA	0.9	0.94 (0.12-7.17)
Humerus fracture	bDMARD naïve	13	3263.4	4.0	Reference
	bDMARD user	13	3425.2	3.8	1.00 (0.17-5.80)
Forearm fracture	bDMARD naïve	17	3228.6	5.3	Reference
	bDMARD user	19	3408.7	5.6	0.94 (0.42-2.08)
Moderate-High (DAS28-CRP score ≥3.2)					
Osteoporotic fractures	bDMARD naïve	173	12,157.0	14.2	Reference
	bDMARD user	182	15,347.0	11.9	0.94 (0.75-1.18)
Hip fracture	bDMARD naïve	42	12,559.3	3.3	Reference
	bDMARD user	41	15,785.3	2.6	0.89 (0.55-1.44)
Clinical vertebral fracture	bDMARD naïve	21	12,631.3	1.7	Reference
	bDMARD user	21	15,857.9	1.3	0.99 (0.46-2.15)
Humerus fracture	bDMARD naïve	40	12,514.9	3.2	Reference
	bDMARD user	55	15,713.4	3.5	1.13 (0.71-1.80)
Forearm fracture	bDMARD naïve	90	12,403.9	7.3	Reference
	bDMARD user	83	15,669.3	5.3	0.87 (0.60-1.24)

bDMARD = biological disease-modifying antirheumatic drug; CI = confidence interval; CRP = C-reactive protein; DAS28-CRP = Disease Activity Score in 28 joints with C-reactive protein; IR = incidence rate; py = person-years.

Supplementary Table S3 Sensitivity Analysis, Evaluating Osteoporotic Fracture Risk Associated by bDMARD Use in Rheumatoid Arthritis Patients Compared with No Biological Use in Propensity-Score Matched Analysis, Stratified by Fracture Type, only by Excluding Patients with a Fracture in the 1-Year Prior (N = 9332)

By fracture type	Patient group	Number of fractures	Py	IR per 1000 py	Hazard ratio (95% CI)
Osteoporotic	bDMARD naïve	257	16,843.0	15.3	Reference
	bDMARD user	280	20,379.0	13.7	0.91 (0.74-1.12)
Hip	bDMARD naïve	70	17,426.0	4.0	Reference
	bDMARD user	58	21,079.9	2.8	0.75 (0.52-1.09)
Clinical vertebral	bDMARD naïve	27	17,552.3	1.5	Reference
	bDMARD user	28	21,173.2	1.3	1.12 (0.48-2.63)
Humerus	bDMARD naïve	67	17,380.8	3.9	Reference
	bDMARD user	93	20,938.5	4.4	1.14 (0.78-1.66)
Forearm	bDMARD naïve	122	17,234.2	7.1	Reference
	bDMARD user	130	20,868.8	6.2	0.85 (0.63-1.16)

bDMARD = biological disease-modifying antirheumatic drug; CI = confidence interval; IR = incidence rate; py = person-years.