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Effects of Disease-Modifying Antirheumatic Drugs on Non-Vertebral Fracture Risk in Rheumatoid Arthritis: a Population-based Cohort Study

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Abstract

Objective—Several prior investigations demonstrate an improvement in bone mineral density associated with use of TNF inhibitors (TNFi). We compared the risk of osteoporotic fractures among patients with rheumatoid arthritis (RA) initiating a disease-modifying antirheumatic drug (DMARD).

Methods—A population-based cohort study was conducted using health care utilization data (1996–2008) from a Canadian province and a US commercial insurance plan. Patients with at least two RA diagnoses were identified and follow-up began with the first prescription for a DMARD. Drug regimens were categorized into three mutually exclusive hierarchical groups: 1) TNFi with or without non-biologic DMARDs (nbDMARD), 2) methotrexate (MTX) without a TNFi, or 3) other nbDMARD without a TNFi or MTX. Main outcomes were hospitalizations for fractures of the hip, wrist, humerus, or pelvis based on diagnoses and procedure codes.

Results—The study cohort consisted of 16,412 RA patients with 25,988 new treatment episodes: 5,856 TNFi, 12,554 MTX, and 7,578 other nbDMARD. The incidence rate per 1,000 person-years for osteoporotic fracture were 5.11 (95% CI 3.50–7.45) for TNFi, 5.35 (95% CI 4.08–7.02) for MTX, and 6.38 (95% CI 3.78–10.77) for other nbDMARD. After multivariable adjustment for osteoporosis and fracture-related risk factors, the risk of non-vertebral osteoporotic fracture was not different in either TNFi (hazard ratio (HR) 1.07, 95% CI 0.57–1.98) or MTX (HR 1.18, 95% CI 0.60–2.34) compared with nbDMARD.

Conclusion—Among subjects diagnosed with RA, the adjusted risk of non-vertebral fracture was similar across persons starting a TNFi, MTX, or other nbDMARD.

Keywords

rheumatoid arthritis; fracture; disease modifying antirheumatic drugs

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Competing interests

Kim has received research support from Takeda Pharmaceuticals North America and Pfizer. Schneeweiss is a paid member of scientific advisory boards for HealthCore and has received consulting fees from WHISCON. Schneeweiss received research grants from Pfizer and Novartis.

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INTRODUCTION

Rheumatoid arthritis (RA) is associated with an increased risk of osteoporosis and fractures. (1–3) A recent population-based cohort study reported that patients with RA had a 25% higher risk of osteoporotic fracture compared with non-RA subjects.(1) A number of factors such as older age, female sex, menopause, lower body mass index (BMI), glucocorticoids use, high RA disease activity, long RA disease duration, and decreased physical activity are associated with an increased risk of osteoporosis.(2, 4–7) Several studies demonstrated a link between proinflammatory cytokines such as tumor necrosis factor (TNF)- α , interleukin-1 and 6, and osteoporosis.(6, 8–10) These cytokines play an important role in bone resorption by stimulating osteoclast differentiation and increasing osteoclast activation. They also potentially lead to bone loss by inhibiting bone formation.(11–13) Some epidemiologic studies, but not all, also note a positive correlation between osteoporosis and C-reactive protein (CRP) which is a marker of active inflammation.(9, 14–16)

The relationship between RA, inflammation and osteoporosis suggests that systemic immunosuppression with disease-modifying antirheumatic drugs (DMARDs) may reduce the risk for osteoporosis and osteoporotic fracture in patients with RA. There is limited data regarding the effect of different DMARD agents, either biologic or non-biologic, and bone metabolism in patients with RA. Furthermore, results from several small studies that examined a potential effect of methotrexate (MTX) or tumor necrosis factor- α inhibitors (TNFi) on the hip, spine, or hand bone mineral density (BMD) were not consistent.(15, 17–28) Little is known about whether use of DMARDs has any impact on the risk of non-vertebral osteoporotic fracture in patients with RA.

We examined the relationship between different DMARD medications and the risk of non-vertebral osteoporotic fracture among RA patients using administrative data from two large health care insurance programs - one Canadian and one US. Based on prior studies suggesting improved BMD with TNFi, we hypothesized that TNFi would decrease the risk of non-vertebral osteoporotic fracture in RA patients compared to non-biologic DMARD (nbDMARD).

MATERIALS & METHODS

Study Design

We conducted a cohort analysis of the risk of osteoporotic fracture among subjects with RA initiating a DMARD. Subjects were enrolled in a Canadian Provincial health care system or a commercial US health plan. The Canadian Provincial health care system includes all persons living in the Province and is considered population-based. The US commercial plan insures mainly working adults and a small Medicare managed care population. The study protocol was approved by the Partners Healthcare Institutional Review Board.

Study Cohort

Potentially eligible subjects were over 18 years of age and diagnosed with RA, based on at least two inpatient or outpatient visits coded with the ICD-9-CM 714.XX. Continuous enrollment in the health plan for 12 months prior to the second diagnosis of RA was required. All persons in the study cohort were required to have had two diagnoses and at least one filled prescription for a DMARD at the start of follow-up. Subjects entered the study cohort at the first change in DMARD regimen. Algorithms to define RA in a large health care utilization database that requires both two diagnoses and one or more dispensing of DMARDs have been found to have a positive predictive value of 86% for RA.(29) Our study spanned the period January 1996 through June 2008. Subjects were followed until they experienced an outcome, died, disenrolled from the health plan, or follow-up ended.

Exposure Definitions

We defined three mutually exclusive groups of DMARDs: TNFi, MTX, and other nbDMARD (i.e., hydroxychloroquine, sulfasalazine, leflunomide, cyclosporine, azathioprine, cyclophosphamide, mycophenolate mofetil, 6-thioguanine, d-penicillamine, gold, auranofin, myochrysine, and solganol). The TNFi group included adalimumab, etanercept, or infliximab. The MTX group included oral or injectable MTX. Subjects in the TNFi group were on a TNFi with and without non-biologic DMARDs including MTX. Subjects in the MTX group could not simultaneously use a TNFi; however, they could use other nbDMARDs. The other nbDMARD group, chosen as a reference, could not simultaneously use a TNFi or MTX or any other biologic systemic immunosuppressive drug. Study follow-up began with entry into one of these three exposure groups. Because the timing of the potential effect of DMARDs on fracture is not clear, our primary analysis permitted persons to enter the study cohort more than once and considered them in a given exposure group during the period of an active prescription. These assumptions were tested in a sensitivity analysis, in which we only allowed subjects to enter the cohort once.

Outcome Definitions

The primary outcome was defined as a fracture of the hip, wrist, humerus or pelvis, because these are considered to be typical sites of non-vertebral osteoporotic fracture and can be accurately defined in administrative claims databases.(30) The definitions of fracture were based on a combination of inpatient or outpatient diagnoses and procedure codes contained within the study database (see Appendix 1). Patients were censored at their first fracture in the ‘any osteoporotic fracture’ analysis for a given exposure group.

Covariates

Variables potentially related to a future fracture were assessed using data from the 12 months before the index date. These variables included demographic factors (age and sex), osteoporosis-related factors (osteoporosis diagnosis, osteoporosis medications, prior fractures, presence of BMD tests, Parkinson’s disease, Alzheimer’s disease, prior falls, and other comorbidities), use of other medications likely associated with bone metabolism or fall risk (oral glucocorticoids, anticonvulsants, benzodiazepines, selective serotonin reuptake inhibitors (SSRIs), proton pump inhibitors (PPIs), beta blockers, and opioids), and health care utilization factors (number of physician visits, acute care hospitalizations, and number of different medications). To quantify patients’ comorbidities, we calculated the Deyo-adapted Charlson Comorbidity Index based on ICD-9-CM.(31–32) The Comorbidity Index is a summary score, based on the presence of 19 major medical conditions including myocardial infarction, pulmonary, renal, hepatic disease, diabetes, cancer, human immunodeficiency virus infection, etc. A score of 0 represents absence of these comorbidities and a higher score indicates a greater number of comorbid conditions.

Statistical Analyses

We compared the baseline characteristics across the three exposure groups. Fracture of the hip, wrist, humerus or pelvis (‘osteoporotic fracture’) was identified during follow-up and person-years calculated from the start of follow-up until occurrence of fracture or other censoring events. The incidence rate (IR) and hazard ratio (HR) and 95% confidence interval (CI) for fracture was estimated for each exposure group.

The HR of composite osteoporotic fracture was estimated in a series of Cox proportional hazard models with increasing adjustment: Model 1 was adjusted for age and sex; Model 2 was adjusted for age, sex and prior use of steroid; and Model 3 was additionally adjusted for osteoporosis-related risk factors, cumulative steroid dose, use of other drugs such as oral

glucocorticoids, anticonvulsants, benzodiazepines, SSRIs, PPIs, beta blockers, and opioids, Charlson Comorbidity Index, and health care utilization characteristics. These covariates were defined using data from the 12 months before the start of study follow-up. No information was available on BMI, BMD, or frailty. We performed the Kolmogorov supremum test to check the proportional hazards assumption for each of the Cox regression models.(33)

Sensitivity analyses included the variations on exposure definition as noted above. Other sensitivity analyses were performed by including only 1) subjects with a follow up period of 90 days or longer as a lag time period; 2) female subjects only; 3) persons with prior glucocorticoid use; 4) persons without prior glucocorticoid use; and 5) focusing only on those without a prior fracture.

RESULTS

We found 116,321 potentially eligible subjects with at least two visits for RA (see Figure 1). From this group, we excluded persons without a 365-day eligibility period prior to cohort entry (n=34,614) or evidence in the database of use of a systemic immunosuppressive drug (n = 65,295). Our final study cohort consisted of 16,412 subjects with 25,988 new treatment episodes.

Baseline characteristics of the three exposure groups are shown in Table 1. The groups were similar with respect to age, gender, prior fracture and falls, use of osteoporosis medication, number of different medications used, comorbidities, and number of physician visits. Use of oral glucocorticoid in 30 days before the index date as well as the mean cumulative dose of oral glucocorticoids in 12 months before the index date was greater in the TNFi group compared to the MTX or other nbDMARD group. Use of other medications such as benzodiazepines, opioids and PPIs was also higher in the TNFi group compared to the MTX or other nbDMARD group.

The IR for osteoporotic fracture at any of four sites, hip, humerus, pelvis, and wrist, was 6.38 (95% CI, 3.78–10.77) per 1,000 person-years for persons who started other nbDMARD, 5.38 (95% CI, 4.08–7.02) per 1,000 person-years for MTX and 5.11 (3.50–7.45) per 1,000 person-years for a TNFi (see Table 2).

Table 3 contains the HRs for fracture at each anatomical location in multivariate models. After full multivariable adjustment controlling for osteoporosis and fracture-related factors, the risk of osteoporotic fracture was not different in either TNFi (1.07, 95% CI 0.57–1.98) or MTX (1.18, 95% CI 0.60–2.34) initiators, compared with nbDMARD. No significantly elevated risks were noted across four different anatomical sites.

For the composite outcome, osteoporosis fracture at any of four sites, neither the partially (Models 1 and 2) nor the fully adjusted (Model 3) models suggest a reduced relative risk in patients initiating a TNFi and MTX compared with other nbDMARD (see Appendix 2).

None of the sensitivity analyses (see Figure 2) showed a decreased relative risk of non-vertebral osteoporotic fracture for RA patients initiating a TNFi compared to nbDMARD. We also performed a sensitivity analysis that allowed a subject to enter the cohort only once. 3,438 subjects started a TNFi, 9,461 MTX, and 3,513 other nbDMARD. The HR of osteoporotic fracture was 1.28 (95% CI, 0.56–2.95) for TNFi initiators and 0.85 (95% CI, 0.40–1.83) for MTX compared to other nbDMARD. For every model, the result of the Kolmogorov-type supremum test was not significant (all p-values > 0.80). Therefore, the "proportional hazards assumption" was not violated in our models.

DISCUSSION

RA is associated with focal bone erosions at the joint and systemic bone loss, osteoporosis. Although the bone resorption process in RA is not fully understood, it has been shown that TNF α as well as the ligand for receptor activator of NF- κ B (RANKL) have regulatory effects on osteoclastogenesis in RA, leading to development of bone erosion.(34) Chronic inflammation, mediated by these proinflammatory cytokines, is thought to increase the risk of osteoporosis and fracture in RA.(10) We examined the risk of osteoporotic fracture associated with a variety of DMARDs used for RA, because there is a possibility that use of systemic immunosuppressants such as DMARDs may reduce the risk of osteoporosis and there is limited data available for the risk of osteoporotic fracture in patients with RA relative to their treatment. The main finding of this study is, however, that osteoporotic fracture risk was not reduced in RA patients initiating a TNFi or MTX, compared to those starting other nbDMARD. Results from a variety of sensitivity analyses were also similar.

In our study, a fully adjusted HR was 1.07 (95% CI 0.57–1.98) in patients starting MTX compared to other nbDMARD. MTX was previously thought to have detrimental effects on bone, described by the term ‘MTX osteopathy’, mostly reported in children who had had a long-term maintenance therapy of MTX for acute leukemia.(35–36) Conflicting data, however, exists on the effect of low dose MTX in patients with rheumatic disease. Several case series reported stress fracture in tibia or fibula in patients with rheumatic disease on MTX,(37–38) while some found no association between low dose MTX use and change in femoral neck or lumbar spine BMD in RA patients.(17, 39–40) Low dose MTX use was not associated with change in femoral neck or lumbar spine BMD in patients who were not treated with corticosteroids, whereas combined treatment with MTX and 5mg or more prednisone per day was associated with greater bone loss in the lumbar spine than treatment with prednisone without MTX.(17)

Some data exists on a potential beneficial role of TNFi in bone loss,(41) and several published studies have examined BMD changes among patients with RA initiating a TNFi. (see Table 4) Most of the studies were observational and included only a small number of patients on a TNFi, mostly infliximab, and did not have a comparison group. The duration of follow up was generally short, varying from 6 months to 3.5 years. A number of studies reported improvement in the spine or hip BMD among TNFi users,(21, 23, 25) while others reported either stable BMD or less bone loss in TNFi users.(18–19, 22, 24, 26–28, 42–44) Although the exact role of TNFi on BMD remains unknown, one might still believe that BMD improved or did not decrease with use of TNFi.

Why did this current study then not observe similar effects on the risk of fracture? Even if a TNFi increases BMD in RA patients to some degree, it is possible that such improvement in BMD does not fully lead to lowering fracture risk in this patient population at high risk of osteoporosis and fracture. Several limitations in our study might also provide potential explanations. First, this cohort study is likely subject to residual confounding by race, family history of osteoporosis, BMD, BMI, calcium and vitamin D intake, frailty, physical activity, and other unmeasured risk factors. Although we assessed variables potentially related to a future fracture using the data from the 12 months prior to the index date, this time period might not be long enough to capture all the information on potential confounders.

Use of corticosteroids was adjusted as both the cumulative dose of oral corticosteroids in 12 months before the index date and any use of oral corticosteroids in 30 days before the index date. Steroid use during the follow-up period was not adjusted in our analysis. A recent study, however, showed that the use of medications (i.e., steroids or non-steroidal anti-inflammatory drugs) to control symptoms increased in the 6 months immediately before a

new DMARD regimen was initiated compared to the previous 6–12-month period and that there was only modest change in the use of corticosteroids in 6–12 months after initiation of DMARDs.(45)

Second, as true in most epidemiologic studies, patients were not randomly exposed to drugs in our study. Therefore, the possibility of confounding by indication cannot be excluded with regard to the effect of different DMARDs on fracture risk in patients with RA. Large longitudinal RA registries either in Europe or the US might be an alternative choice for data source to study comparative safety or effectiveness although it is still subject to unmeasured confounding or confounding by indication.(46) One could completely avoid the issue of confounding bias by conducting a randomized clinical trial (RCT) (47). However, there are a number of important limitations in RCTs, including insufficient sample sizes, inadequate follow-up time, generalizability, ethical issues, and substantial cost, to study a relatively uncommon, long-term safety outcome of drugs such as fracture. It is highly unlikely that there will be a head-to-head randomized clinical trial of DMARDs that can address such safety outcome.

Third, there could be misclassification with the diagnoses of RA and osteoporotic fractures as we mainly relied on diagnosis and procedure codes to identify them although both the ICD codes for RA and fracture and procedure codes for fractures have been used a number of studies.(1, 30, 48)

Lastly, it is possible that our study had inadequate power to detect an increased the risk of osteoporotic fracture related to use of TNFi or MTX compared to other nbDMARD. Even with the use of a large cohort of RA patients from the combined data set (N= 16,412), it is challenging to investigate the risk of a relatively uncommon outcomes (fractures). Our results show that we can exclude an increase in the rate of osteoporotic fracture by more than 100% in TNFi and 135% in MTX initiators compared to nbDMARD initiators, with a confidence level of 95%.(49)

Several strengths of the current study are also worth noting. Our study provides novel information on treatment-specific fracture risk in RA patients using data from a population that is representative of the U.S. commercially-insured population and a Canadian Province. The study databases comprise many thousand patients from various settings, allowing us to better generalize from the findings of a specific study. Despite the aforementioned limitations such as unmeasured confounding or misclassification, our results were simultaneously adjusted for more than 20 risk factors of osteoporotic fracture in the multivariable Cox models and remained consistent across different patient subgroups in various sensitivity analyses. We used pharmacy claims information to identify initiators of different DMARD agents, which is thought to be more accurate than the use of medical records or patient-report.(50) Furthermore, the new user design employed in the present study, in which exposure time begins with the start of a new systemic immunosuppressive, allows for a more valid comparison of treatments than mixing ongoing users with new users in the same analysis.(51)

In conclusion, our study showed that the adjusted risk of fracture was similar across patients with RA starting a TNFi, MTX, or other nbDMARD. Various sensitivity analyses also yielded consistent results. Future studies using a detailed clinical dataset from large prospective RA cohorts or randomized clinical trials of DMARDs with long-term follow up periods could provide further information in fracture risk in RA patients relative to different DMARDs.

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Appendix 1

Definition of fracture outcomes

Fracture	Definition
Humerus	Humerus fracture diagnosis (ICD-9: 812.xx, 733.11) AND procedure within 30 days of fracture date (ICD-9: 78.52, 79.01, 79.11, 79.21, 79.31, 79.61; CPT-4: 23600, 23605, 23610, 23615, 23620, 23625, 23630, 23665, 23670, 23680, 24500, 24505, 24506, 24510, 24515, 24530, 24531, 24535, 24536, 24538, 24540, 24542, 24545, 24560, 24565, 24570, 24575, 24581, 24583, 24585-8, 24516)
Wrist	Radius/ulna fracture diagnosis (ICD-9: 813.xx, 733.12) AND procedure within 30 days of fracture date (ICD-9: 78.53, 79.02, 79.12, 79.22, 79.32, 79.62; CPT-4: 24620, 24625, 24635, 24650, 24655, 24660,

Fracture	Definition
	24665-6, 24670, 24680, 24685, 25500, 25505, 25510, 25515, 25530, 25535, 25540, 25545, 25560, 25565, 25570, 25575, 25600, 25605, 25610-1, 25615, 25620, 25650)
Hip	Hip fracture diagnosis (ICD-9 code: 820.xx,733.14) during hospitalization AND procedure code during hospitalization (ICD-9: 78.55, 79.05, 79.15, 79.25, 79.35, 79.65; CPT-4: 27230–27248)
Pelvis	Pelvis fracture diagnosis (ICD-9: 808.xx)

ICD-9: International Classification of Diseases –9; CPT-4: Current Procedural Terminology –4

Appendix 2

Adjusted Cox proportional hazard ratios (95% confidence interval) for risk of osteoporotic fracture in rheumatoid arthritis

	TNF inhibitor	Methotrexate	Other non-biologic DMARD
Model 1	1.27 (0.80–2.00)	0.77 (0.51–1.17)	1.00
Model 2	1.20 (0.76–1.91)	0.80 (0.53–1.21)	1.00
Model 3	1.18 (0.60–2.34)	1.07 (0.57–1.98)	1.00

TNF: tumor necrosis factor, DMARD: disease-modifying antirheumatic drug

Model 1: Adjusted for age and sex. Model 2: Adjusted as Model 1 + baseline steroid use. Model 3: Adjusted as Model 2 + diagnosis of osteoporosis, Alzheimer's dementia, Parkinson disease, prior fall, prior fracture, use of osteoporosis drugs, anticonvulsants, benzodiazepines, opioids, selective serotonin reuptake inhibitors, and proton pump inhibitors, and Charlson Score.

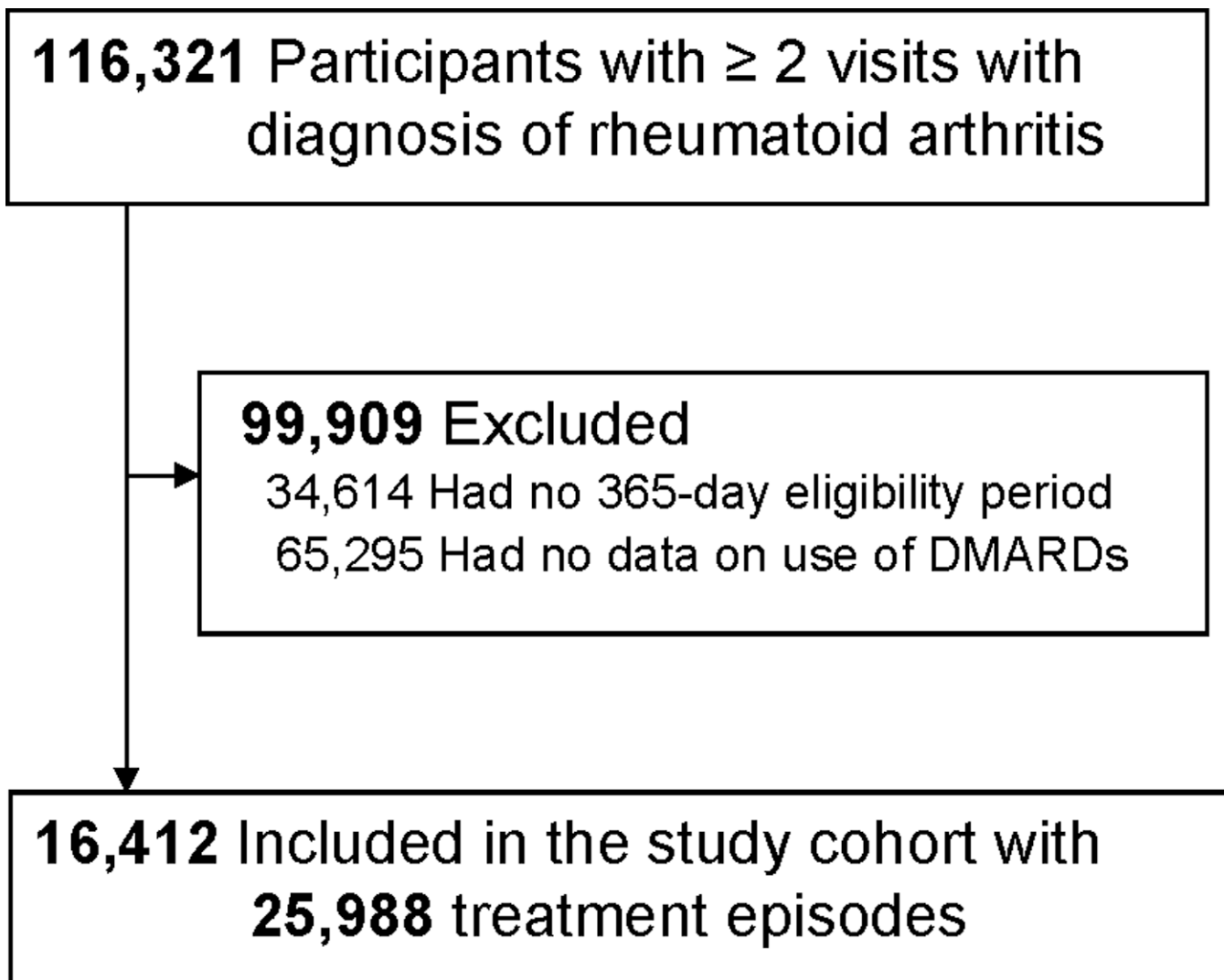


Figure 1. Study cohort selection
DMARD: disease-modifying antirheumatic drug

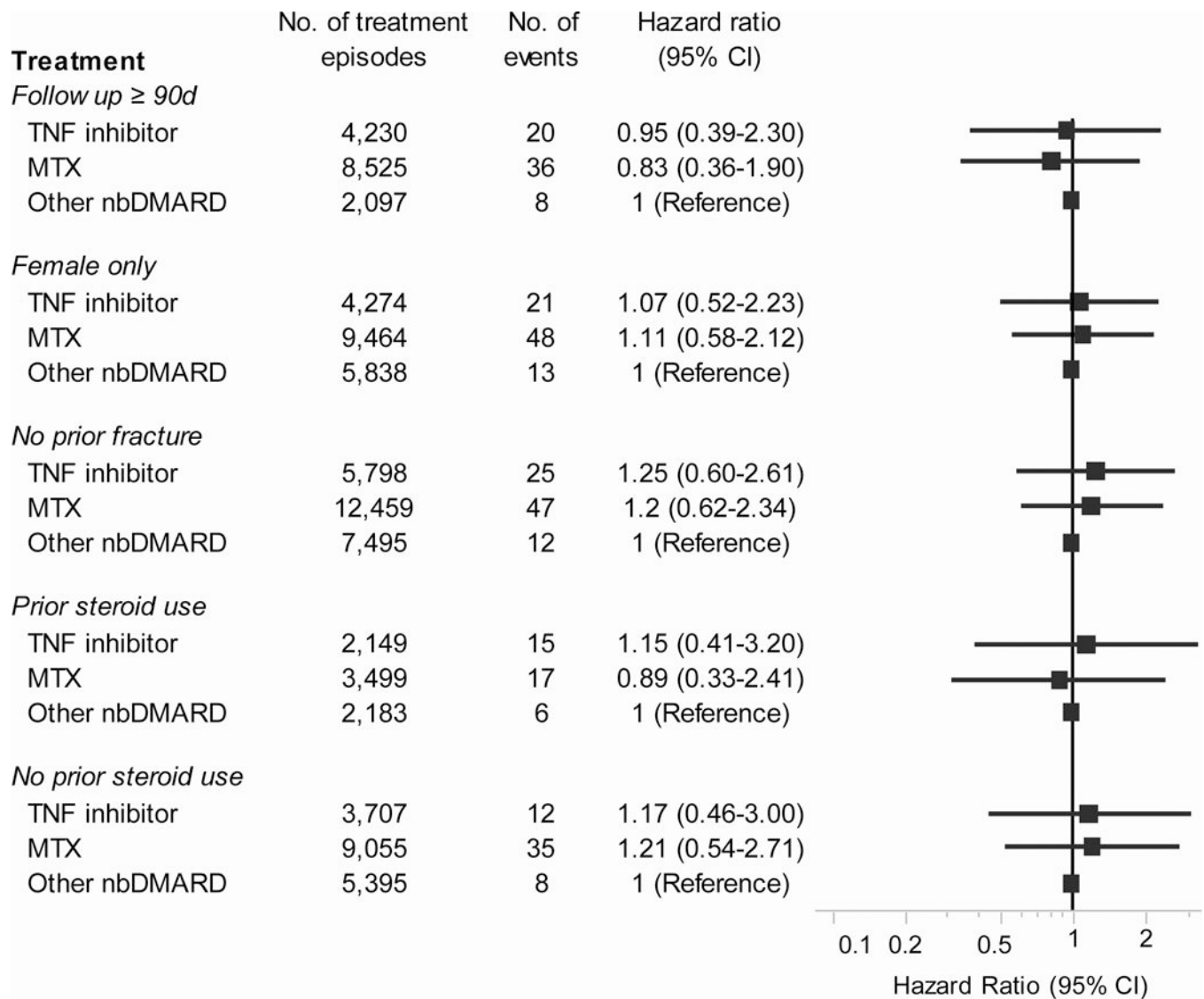


Figure 2. Sensitivity Analyses

TNF: tumor necrosis factor, MTX: methotrexate, nbDMARD: non-biologic disease-modifying antirheumatic drug, CI: confidence interval

Table 1

Baseline characteristics of the study cohort in 12 months before the index date

	TNF inhibitor	Methotrexate	Other non-biologic DMARD
No. of treatment episodes	5,856	12,554	7,578
Demographic			
Age, mean (SD), years	52.5 (13.4)	55.6 (13.3)	55.2 (13.0)
Female	4,274 (73.0)	9,464 (75.4)	5,838 (77.0)
Osteoporosis-related			
Osteoporosis diagnosis	840 (14.3)	1,429 (11.4)	1,133 (15.0)
Osteoporosis medication	1,129 (19.3)	2,372 (18.9)	1,535 (20.3)
Prior fracture	58 (1.0)	95 (0.8)	83 (1.1)
Bone mineral density test	860 (14.7)	1,655 (13.2)	1,056 (14.0)
Parkinson's disease	10 (0.2)	23 (0.2)	8(0.1)
Alzheimer's disease	2 (0.03)	4 (0.03)	7 (0.09)
Prior fall	71 (1.2)	143 (1.1)	115 (1.5)
Comorbidity Index, mean (SD) ^a	1.63 (1.4)	1.68 (1.6)	1.74 (1.5)
Medication use			
Recent use of oral glucocorticoids ^b	2,149 (36.7)	3,499 (27.9)	2,183 (28.8)
Cumulative dose of oral glucocorticoids, mean (SD) ^c	659.7 (1605.4)	415.6 (1077.7)	526.59 (1465.3)
Anticonvulsants	381(6.5)	673 (5.4)	575 (7.6)
Benzodiazepines	945 (16.1)	1663 (13.3)	1,184 (15.6)
SSRIs	968 (16.5)	1746 (13.9)	1,184(15.6)
Proton pump inhibitors	1,440 (24.6)	2,455(19.6)	1,702 (22.5)
Beta blockers	686 (11.7)	1,483 (11.8)	968 (12.8)
Opioids	2,515 (43.0)	3,688 (29.4)	2,725 (36.0)
Health care utilization			
Number of physician visits, mean (SD)	17.4 (13.3)	17.3 (13.1)	17.7 (13.6)
Hospitalizations	939 (16.0)	1,778 (14.2)	1,302 (17.2)
Number of all prescription drugs, mean (SD)	11.9 (6.4)	10.8 (6.2)	11.9 (6.7)

TNF: tumor necrosis factor, DMARD: disease-modifying antirheumatic drug Data are expressed as number (%).

SSRI, selective serotonin re-uptake inhibitor

^aCharlson-Deyo Comorbidity Index (31); a score of 0 represents absence of comorbidity and higher scores indicate a greater burden of comorbidity

^bUse of any oral glucocorticoids in 30 days prior to the index date

^ccumulative dose of oral glucocorticoids in 12 months prior to the index date in milligrams

Table 2

Incidence rates (IR) of osteoporotic fracture by fracture site and DMARD use

Fracture site	TNF inhibitor			Methotrexate			Other non-biologic DMARD		
	Fractures, N	Person-years	IR (95% CI)	Fractures, N	Person-years	IR (95% CI)	Fractures, N	Person-years	IR (95% CI)
Any site	27	5285.2	5.11 (3.50–7.45)	52	9712.6	5.35 (4.08–7.02)	14	2194.4	6.38 (3.78–10.77)
Hip	7	5302.9	1.32 (0.63–2.77)	7	9739.1	0.72 (0.34–1.51)	5	2199.2	2.27 (0.94–5.45)
Humerus	7	5299.5	1.32 (0.63–2.77)	7	9739.0	0.72 (0.34–1.51)	2	2202.6	0.91 (0.23–3.64)
Pelvis	7	5301.3	1.32 (0.63–2.77)	23	9730.7	2.36 (1.57–3.55)	5	2201.5	2.27 (0.94–5.45)
Wrist	9	5299.8	1.70 (0.88–3.27)	16	9733.2	1.64 (1.00–2.68)	4	2201.9	1.82 (0.68–4.85)

TNF: tumor necrosis factor, DMARD: disease-modifying antirheumatic drug, CI: confidence interval; IRs are presented per 1,000 person-years.

Table 3

Adjusted Cox proportional hazard ratios (95% confidence interval) of osteoporotic fracture in rheumatoid arthritis by fracture site and DMARD use ^a

	TNF inhibitor	Methotrexate	Other non-biologic DMARD
<i>Fracture site</i>			
Any site	1.18 (0.60–2.34)	1.07 (0.57–1.98)	1.00
Hip	0.65 (0.18–2.32)	0.44 (0.13–1.54)	1.00
Humerus	2.87 (0.56–14.62)	1.18 (0.23–5.90)	1.00
Pelvis	1.11 (0.32–3.82)	1.25 (0.44–3.57)	1.00
Wrist	1.22 (0.35–4.19)	1.24 (0.39–3.92)	1.00

TNF: tumor necrosis factor, DMARD: disease-modifying antirheumatic drug

^aAdjusted for age, sex, baseline steroid use, diagnosis of osteoporosis, Alzheimer's dementia, Parkinson disease, prior fall, prior fracture, use of osteoporosis drugs, anticonvulsants, benzodiazepines, opioids, selective serotonin reuptake inhibitors, and proton pump inhibitors, and Charlson Score.

Table 4
Summary of published studies for the effect of tumor necrosis factor- α inhibitors on bone mineral density in RA patients

Study, Yr	Subjects on TNFi	Mean age (yr)	Subjects on Comparator DMARD	Follow up period	Findings
Lange, 2005(23)	26 IFX	54	-	1 year	BMD increased by 12% at the femoral neck and 3% at the lumbar spine
Vis, 2005(27)	36 IFX	53	-	1 year	BMD remained stable at the spine and hip
Vis, 2006(26)	102 IFX	53	-	1 year	BMD remained stable at the spine and hip
Seritolo, 2006(25)	11 ETA and 10 IFX	51	10 MTX	6 months	BMD increased by 0.1–0.2% at the spine and hip among TNFi users and decreased by 0.6–0.8% at the spine and hip among MTX users
Marotte, 2007(44)	90 IFX	51	99 MTX	1 year	BMD decreased by 2.5–3.9% at the spine and femoral neck in the control group, but remained stable in the IFX group
Serelis, 2008(24)	7 ADA and 12 IFX	54	-	1 year	BMD remained stable at the spine
Chopin, 2008(18)	48 IFX	54	-	54 weeks	BMD remained stable at the spine
Haugeberg, 2009(20)	10 IFX	52	10 MTX	1 year	BMD loss was significantly less in the infliximab group compared with the placebo group at the femoral neck (–0.4% vs. –3.4%) and total hip (–0.2% vs. –2.6%) but not at the hand and spine
Wijbrandts, 2009(28)	52 ADA	51	-	1 year	BMD remained stable at the spine and femur neck
Hoff, 2009(22)	522 ADA	52	246 MTX	104 weeks	Hand BMD loss was lowest in the ADA plus MTX group and greatest in the MTX group (–3.0% vs. –4.6%)
Güller-Yüksel, 2009(19)	52 IFX	54	166 on other treatment	2 years	Hand BMD loss was less in the IFX group compared with other treatment only
Eekman, 2011(21)	52 IFX	60	-	3.5 years	BMD was stable at the hip, increased by 2.6% at the spine, and decreased by 3.1% in the hand
Hoff, 2011(43)	214 ADA	52	188 MTX	2 years	Hand bone loss was less in the ADA plus MTX group, independently of clinically assessed disease activity

TNFi: tumor necrosis factor- α inhibitor; BMD: bone mineral density; IFX: infliximab, ADA, adalimumab, ETA: etanercept, MTX: methotrexate, DMARD: disease-modifying antirheumatic drug