The Risk of Hospitalized Infection in Patients with Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To determine whether patients with rheumatoid arthritis (RA) are at increased risk of hospitalized infection and whether the risk varies by RA treatment.

Methods. A retrospective cohort study was conducted using data from a medical and pharmacy claims managed-care database from 1999 to 2006. A total of 24,530 patients were included in the RA cohort; a random sample of non-RA patients served as a comparison cohort (n = 500,000). Rates of hospitalized infection were compared between the cohorts. A nested case-control analysis was performed within the RA cohort to assess the effect of current RA medication use on hospitalized infection risk.

Results. A total of 1,993 patients with RA and 11,977 non-RA patients experienced a hospitalized infection. The rate of first hospitalized infection was higher in the RA cohort [adjusted hazard ratio = 2.03; 95% confidence interval (CI) 1.93–2.13]. In the case-control analysis, the current use of biological disease modifying antirheumatic drugs (DMARD) was associated with slightly increased risk of hospitalized infection [rate ratio (RR) = 1.21; 95% CI 1.02–1.43]. Methotrexate and hydroxychloroquine were associated with decreased risk. Oral corticosteroid use increased risk (RR = 1.92; 95% CI 1.67–2.21), and there was a dose-related effect [≤ 5 mg/day: RR = 1.32 (95% CI 1.06–1.63), 6–10 mg/day: RR = 1.94 (95% CI 1.53–2.46), > 10 mg/day: RR = 2.98 (95% CI 2.41–3.69)].

Conclusion. These data confirm that individuals with RA are at increased risk of hospitalized infection compared to those without RA. Oral corticosteroid use was associated with a dose-related increase. Biological DMARD use was associated with slightly elevated risk; however, this may reflect confounding and channeling bias. (First Release Feb 1 2008; J Rheumatol 2008;35:387–93)

Key Indexing Terms:
RHEUMATOID ARTHRITIS — INFECTION
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Patients with rheumatoid arthritis (RA) generally experience a range of detrimental health effects as a result of multiorgan disease activities, including functional limitation, physical disability, and excess mortality, in addition to signs and symptoms associated with the disease. The autoimmune expression of the disease is thought to increase the patient's susceptibility for the development of infections. Epidemiological studies suggest that patients with RA have an increased proportionate mortality from infection compared to the general population[1-3]. Few studies, however, have examined the risk of nonfatal infections in patients with RA and compared it with that in the general population. Doran, *et al* found a significantly increased risk of infection[4]; however, other studies have not found evidence of differences between patients with RA and non-RA patients, although methodologic differences may explain some of the discrepancies[5,6].

Any increased risk of infection in patients with RA could be related to intrinsic immunologic disturbances associated with RA itself or to the iatrogenic effects of therapeutic agents. The immunosuppressive function of glucocorticoids that nonspecifically suppress proinflammatory cytokines and

newer biological agents that specifically suppress these cytokines makes infections a central concern. The majority of placebo-controlled clinical trials of newer biological agents and open-label extension periods of these trials did not document an unacceptably high additional morbidity related to infection in those treated with tumor necrosis factor (TNF)-blockade[7-13]. Case reports have suggested an association of the TNF-α inhibitors with serious infections, notably reactivation of tuberculosis and development of other opportunistic infections[14-20]. Data from clinical trials do not provide sufficient evidence concerning these issues because of small sample sizes and selected study populations in which patients with substantial RA disease activities are studied; further, anecdotal case reports do not include a comparison group or a denominator to allow for the computation of adverse event rates. Recent epidemiologic studies examining the effect of anti-TNF on the risk of infection have shown mixed results[21-26].

Our objectives were to determine whether individuals with RA are at increased risk of hospitalized infection compared to those without RA, and to assess whether the risk of hospitalized infection in patients with RA is higher during the use of newer biological disease modifying antirheumatic drugs (DMARD).

MATERIALS AND METHODS

Data source. The data source for our study was the PharMetrics integrated claims database, which includes information from fully adjudicated pharmacy, provider, and facility claims for members enrolled in 61 health plans across the US. Each claim in the database contains a unique encrypted patient identifier that can be used to assemble a longitudinal record of medical services for each health plan member. Age, sex, and health plan characteristics are collected for all members. Dates of eligibility, including interruptions, are available for the majority (80%) of members, enabling the calculation of person-time at risk. Data available for each medical claim include dates of service, location of service, International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes, physician specialty, and procedure codes in the Physicians' Current Procedural Terminology (version 4) and the Health Care Financing Administration Common Procedure Coding System. Multiple diagnoses and procedures may be recorded for a single outpatient office visit or hospital admission. Data identified with each pharmacy dispensing include the drug dispensed in National Drug Code (NDC) format, the date of dispensing, and the quantity and number of therapy-days dispensed.

Subjects in PharMetrics are representative of the national commercially insured population on a variety of demographic measures including age, sex, geographic region, and health plan type. In order to ensure complete data recording and unbiased samples, only health plans submitting data for all members are included in the database. Contributions are also subjected to a series of rigorous data quality checks to ensure a standardized format and minimize errors. PharMetrics data have been used for various studies in pharmacoepidemiology[27-30].

Study design. We conducted a retrospective cohort study using data collected prospectively in PharMetrics from January 1, 1999, through July 31, 2006, to estimate population-based incidence rates of prespecified infectious outcomes in adult patients with RA and in adults without RA. We compared the rate of hospitalized infection in patients with RA to the rate in non-RA patients, controlling for potential confounders. We examined the relation of medication exposure to hospitalized infection using a nested case-control approach within the RA cohort.

Study subjects. All patients at least 18 years of age who had at least 2 physician visits more than 2 months apart for RA with an ICD-9-CM code of 714 were included in the RA cohort. To further ensure that our RA cohort had RA, the following codes were not included in the RA definition: 714.3 (juvenile chronic polyarthritis), 714.4 (chronic postrheumatic arthropathy), and 714.9 (unspecified inflammatory polyarthropathy). Inclusion criteria for the non-RA cohort was at least 18 years of age at cohort entry and no ICD-9-CM code for RA during followup. Cohort entry was defined by the date of the first RA diagnosis for the RA cohort and first medical claim for the non-RA cohort that occurred after the health plan member had been enrolled in the health plan for at least 180 days or January 1, 1999, whichever was later. Subjects who were missing a value for age or sex, or experienced an outcome of interest in the 90 days prior to cohort entry were excluded from both cohorts. Also excluded were subjects enrolled in plans that provide supplementary insurance to Medicare, because we did not have access to all of their claims. A random sample of 500,000 individuals meeting the inclusion criteria constituted the non-RA cohort.

Person-time and exposure. All subjects were followed from the date of their cohort entry until they experienced the event, were no longer enrolled in the health plan, or July 31, 2006, whichever came first. For subjects without eligibility dates, the date of their last claim was used as a proxy for the end of enrollment. When comparing the rates between individuals with RA and those without RA, the exposure was simply whether or not the subject had RA.

For analyses within the RA cohort, each cohort member's person-time was classified on a person-day basis according to RA medication exposure. Each person's sequence of prescriptions was evaluated to make the best determination of exposure status on each day. For medications identified by procedure codes, duration of exposure was assigned based on the labeling information for the specific medication. For RA medications identified by the NDC on pharmacy claims, the number of days supplied was obtained from the database; for any dispensing for which the days supplied was missing or zero, the median days supplied for other dispensings of that medication was employed (by NDC). For our primary analysis, we assumed full medication adherence such that the length of exposure equaled the number of days of medication the patient received. In sensitivity analyses, we assumed 80% adherence for oral medications, thereby extending the exposure window for these medications, and separately we also classified patients as currently exposed to a certain medication if they had any exposure during the previous 30 days.

DMARD were classified into traditional DMARD and biological DMARD. Traditional DMARD included methotrexate (MTX), azathioprine, tacrolimus, leflunomide, cyclosporine, cyclophosphamide, hydroxychloroquine, sulfasalazine, gold thiomalate, aurothioglucose, auranofin, and penicillamine. Infliximab, etanercept, adalimumab, and anakinra were grouped as biological DMARD. Oral corticosteroid use was also examined, and we categorized daily dosages into 3 categories of prednisone equivalents: ≤ 5, 6–10, and > 10 mg/day.

Outcomes. Outcome events were identified from inpatient and outpatient encounters and operationally defined by specific ICD-9-CM diagnosis codes, NDC and procedure codes. The main outcome of interest was hospitalized infection. For this outcome, our ICD-9-CM diagnosis codes included 001-139, 320-324, 326, 370, 373.4, 373.5, 373.6, 376.01, 381.0-381.4, 382, 383.0, 460-466, 473, 474.0, 480-487, 490, 590, 595, 597, 599.0, 680-684, 686, 711, 730, 790.7, 790.8, 996.6, and 998.5. We defined serious infection as a hospitalized infection or an infection requiring outpatient parenteral antibiotics and evaluated its frequency as a secondary outcome. In a sensitivity analysis, the definition of serious infection was altered to include hospitalized infections and use of any parenteral antiinfective. Exposure status at the time of the outcome was assigned to the medications to which the patient was currently exposed, the assumption being that the outcomes of interest are acute events.

Case-control analysis. All incident cases in the RA cohort were included in the nested case-control analysis, and we defined their case event dates as the index dates. For each case, we formed a risk set of potential controls consisting of all RA cohort members with the same year and quarter of cohort entry and with followup at least as long as that of the case. A random sample of 5 controls was selected from each risk set, and the index date for the controls

was defined such that each control had a followup time that was equal to that of the case. A subject may have been selected as a control more than once, and a future case was eligible to be a control for a prior case.

Analysis

Cohort analysis. Rates of hospitalized infection for the RA and non-RA cohorts were calculated as the number of events divided by the person-time in which the events occurred and are presented as events per 100,000 person-years. Rates in the non-RA cohort were age- and sex-adjusted to the RA cohort. Only the first event was considered. Cox proportional hazards models were used to compare the rate of hospitalized infection between the RA and non-RA cohorts. We adjusted for the following covariates: age (5-year groups), sex, calendar year at cohort entry, number of comorbid conditions, and whether the subject was taking a non-RA prescription medication at cohort entry. The assessment of comorbid conditions was based on diagnoses made during the 180 days prior to cohort entry and was used in an attempt to control for general health. The comorbid conditions considered were those included in the Deyo ICD-9-CM adaptation to the Charlson Comorbidity Index (excluding rheumatologic disease)[31,32].

Case-control analysis. We estimated rate ratios of hospitalized infection for each of the current drug exposures of interest, including biological DMARD, specific traditional DMARD, and oral corticosteroids. In addition, we examined the effect of corticosteroid dose. Conditional logistic regression was used to account for the matched design. Analyses were adjusted according to age and sex. All drugs were included in the models so that we controlled concurrently for other medication use. In an attempt to control for disease severity, we included as dichotomous variables a visit to a rheumatologist between cohort entry and the index date, an orthopedic procedure between cohort entry and the index date, and whether the patient was taking non-DMARD drugs, which are generally prescribed for patients with RA for symptomatic relief, namely nonsteroidal antiinflammatory drugs (NSAID) and cyclooxygenase-2 (COX-2) selective inhibitors. Comorbid conditions that have been shown to be associated with infection in patients with RA (diabetes, organic brain disease, and chronic lung disease) were included in the model as were cancer and the number of hospitalizations between the cohort entry date and the index date.

RESULTS

A total of 24,530 patients were included in the RA cohort. The study patients with RA were older than the 500,000 sample of subjects without RA, and a higher percentage was female (Table 1). The RA cohort was followed for a mean of 26.6 months, while the non-RA cohort had a mean of 23.4 months of followup. The non-RA cohort was less likely to have a comorbid condition noted in the 180 days prior to cohort entry and less likely to be receiving a prescription medication at cohort entry. In the RA cohort, 24% of patients received at least one biological agent during followup, 62% were taking at least one traditional DMARD, and 47% received oral corticosteroids.

There were 1,993 cases of a first hospitalized infection identified in the RA cohort, while 11,977 cases were observed in the non-RA cohort. The rate of a first hospitalized infection was 3864.3 per 100,000 person-years for patients with RA. For individuals without RA, the unadjusted rate of a first hospitalized infection was 1249.7 per 100,000 person-years. Adjusted to the age and sex distribution of the US population using data from the 2000 census, the rates were 4484.0 and 2193.8 in the RA and non-RA cohorts per 100,000 person-years, respectively. The rates of prespecified infections are shown in Table 2. Pneumonia was the most frequently reported infection in both groups. The Cox proportional hazards models suggested that patients with RA were at a higher risk of hospitalized infection compared to those in the non-RA cohort. Controlling for age, sex, and calendar year only, the hazard ratio between RA and non-RA subjects was 2.31 [95% confidence interval (CI) 2.20–2.43] for hospitalized infection (Table 3). When adding comorbid conditions and prescription medication use to the model, the hazard ratio was 2.03 (95% CI 1.93–2.13). Regression results stratified by sex, age, diabetes, cancer, and presence of comorbid conditions are shown in Table 4. The presence of RA had the greatest effect on the risk of hospitalized infection in younger and healthier individuals.

The nested case-control analysis for hospitalized infection was based on all 1,993 cases of a first hospitalized infection and 9,965 controls within the RA cohort. Table 5 displays the characteristics of the cases and controls. The cases were more likely to be older, diabetic, have chronic lung disease, and to have been hospitalized previously during followup. The adjusted rate ratios (RR) indicating the specific effect of each

Table 1. Patient characteristics.

Variable	Non-RA Cohort, n = 500,000	RA Cohort, n = 24,530
Female, %	56.1	75.7
Age at cohort entry, %		
18–44	57.6	26.5
45–64	39.3	66.3
65+	3.1	7.2
Plan type, %		
Commercial	90.3	83.1
Medicare risk	3.4	8.7
Unknown/other	6.3	8.2
Followup (mo)		
Mean (SD)	23.4 (17.4)	26.6 (16.5)
Median (Q1–Q3)	20.5 (8.3–34.1)	24.6 (13.3–36.3)
No. of comorbid conditions*, %		
0	88.4	77.0
1–2	11.2	21.8
3+	0.4	1.2
Prescription medication use† at cohort entry, %	39.5	59.4
Oral corticosteroid use during followup, % (use at cohort entry)	10.3 (1.05)	46.9 (17.9)
Traditional DMARD†† use during followup, % (use at cohort entry)		
Methotrexate	0.13 (0.03)	43.1 (20.7)
Hydroxychloroquine	0.15 (0.05)	22.9 (12.2)
Sulfasalazine	0.09 (0.04)	8.9 (3.5)
Leflunomide	0.00 (0.00)	9.0 (3.7)
Azathioprine	0.09 (0.04)	2.1 (0.84)
Cyclosporine	0.24 (0.03)	1.9 (0.23)
Biological DMARD use during followup, % (use at cohort entry)		
Etanercept	0.05 (0.01)	14.8 (4.8)
Infliximab	0.03 (0.01)	8.6 (3.6)
Adalimumab	0.00 (0.00)	5.2 (0.61)
Anakinra	0.00 (0.00)	0.8 (0.16)

All figures are % unless indicated. * Based on diagnosis codes during the 180 days prior to cohort entry. † Excluding RA medications; 100% adherence assumed. †† Others < 1% in the RA group. RA: rheumatoid arthritis; DMARD: disease modifying antirheumatic drugs.

Table 2. Incidence rates of hospitalized and serious infections (per 100,000 person-years) (number of cases are shown in parentheses).

Infection	Non-RA*	RA
Hospitalized		
Overall	1679.6 (11,977)	3864.3 (1,993)
Pneumonia	362.4 (2,261)	841.5 (434)
Urinary tract	258.2 (1,574)	484.7 (250)
Skin	171.9 (1,348)	498.3 (257)
Sepsis	153.1 (972)	383.9 (198)
Opportunistic**	23.02 (132)	65.92 (34)
Tuberculosis	9.48 (49)	21.33 (11)
Serious†	3597.6 (26,523)	6028.3 (3,010)

* Age- and sex-adjusted to the RA cohort. ** Includes mycobacteria infection, *P. carinii* pneumonia, nocardiosis, histoplasmosis, coccidioidomycosis, blastomycotic infection, systemic candida, and infections caused by other opportunistic mycoses (i.e., aspergillosis, cryptococcus). † Includes hospitalized infections and infections requiring outpatient parenteral antibiotics. RA: rheumatoid arthritis.

Table 3. Incidence rates and Cox proportional hazards analysis of time to hospitalized infection.

Infection	Non-RA	RA
No. of cases	11,977	1,993
Person-time, yrs	958,371	51,475
Unadjusted rate (per 100,000 person-years)	1249.7	3864.3
Unadjusted hazard ratio (95% CI)	Reference	3.11 (2.96–3.26)
Adjusted hazard ratio (95% CI): Model 1*	Reference	2.31 (2.20–2.43)
Adjusted hazard ratio (95% CI): Model 2†	Reference	2.03 (1.93–2.13)

* Adjusted for age, sex, and calendar year of cohort entry. † Adjusted for age, sex, calendar year of cohort entry, prescription medication use at cohort entry (excluding RA medications), and number of comorbid conditions in the 180 days prior to cohort entry.

current medication exposure, independent of concomitant medication use, are shown in Table 6. The results suggested that current use of biological DMARD was associated with hospitalized infection (RR = 1.21; 95% CI 1.02–1.43). MTX and hydroxychloroquine were associated with a decreased risk; whereas for sulfasalazine, leflunomide, and other traditional DMARD there was no association. Current MTX and biological DMARD use was not associated with decreased risk compared to biological DMARD use alone. The risk of hospitalized infection was most elevated with current exposure to oral corticosteroids (RR = 1.92; 95% CI 1.67–2.21). We also found a dose-related increase; even dosages of ≤ 5 mg/day were associated with hospitalized infection risk (RR = 1.32; 95% CI 1.06–1.63).

Sensitivity analyses indicated that the results were not highly influenced by our assumptions (data not shown). An analysis of serious infections that included hospitalized infections and outpatient parenteral antibiotics as our outcome definition yielded similar rate ratios. Limiting the outcome to only hospitalized infection identified by the primary diagnosis also did not substantially alter our rate ratios. Results were also unaffected when medication exposure windows were lengthened to account for potential nonadherence to medication, when only subjects with at least 6 months of data before cohort entry were analyzed, or when we included use of any parenteral antiinfective as a serious infection.

DISCUSSION

In this large population-based study, we found that patients with RA have approximately a 2-fold increase in the risk of hospitalized infection compared to individuals without RA. Our findings are consistent with those of Doran, *et al*, who found an increased risk of infection requiring hospitalization

Table 4. Rate of hospitalized infection and hospitalized infection risk stratified by patient characteristics.

Characteristic	Rate per 100,000 person-years		Hazard Ratio* (95% CI)		
	Non-RA†	RA	Unadjusted	Adjusted Model 1††	Adjusted Model 2§
Male	1832.2	4053.8	3.26 (2.98–3.58)	2.26 (2.06–2.48)	2.00 (1.82–2.19)
Female	1614.8	3803.0	3.05 (2.89–3.23)	2.39 (2.25–2.53)	2.08 (1.96–2.21)
Age					
18–44	871.8	2387.2	2.93 (2.62–3.27)	2.77 (2.47–3.09)	2.26 (2.02–2.54)
45–64	1399.9	3694.4	2.57 (2.42–2.73)	2.64 (2.48–2.81)	2.19 (2.05–2.33)
65+	7296.6	11988.3	1.61 (1.44–1.79)	1.64 (1.47–1.84)	1.54 (1.38–1.73)
Diabetes**	4866.8	8261.1	1.83 (1.63–2.07)	1.71 (1.51–1.93)	1.52 (1.34–1.72)
No diabetes**	1459.4	3502.4	3.17 (3.01–3.34)	2.39 (2.26–2.52)	2.13 (2.02–2.25)
Cancer**	5262.4	8417.8	1.70 (1.42–2.04)	1.61 (1.34–1.93)	1.40 (1.16–1.68)
No cancer**	1566.7	3711.4	3.13 (2.98–3.29)	2.36 (2.24–2.48)	2.09 (1.98–2.20)
≥ 1 comorbid condition**	4527.9	7570.3	1.92 (1.78–2.07)	1.68 (1.56–1.82)	1.67 (1.54–1.80)
No comorbid condition**	1129.4	2876.0	3.18 (2.99–3.38)	2.51 (2.36–2.68)	2.43 (2.28–2.59)

* Non-RA is reference group. † Rates in the non-RA cohort are adjusted to the age and sex distribution of the RA cohort. †† Adjusted for age, sex, and calendar year of cohort entry. § Adjusted for age, sex, calendar year of cohort entry, prescription medication use at cohort entry (excluding RA medications), and number of comorbid conditions in the 180 days prior to cohort entry. ** Noted in the 180 days prior to cohort entry.

(hazard ratio = 1.8; 95% CI 1.5–2.2), objectively confirmed infection (hazard ratio = 1.7; 95% CI 1.4–2.0), and any documented infection (hazard ratio = 1.5; 95% CI 1.3–1.6) in an inception cohort of 609 patients with RA compared with population-based non-RA subjects[4]. They identified age, extraarticular manifestations of RA, leukopenia, use of corticosteroids, and comorbidities as predictors of infection in the patients with RA[33]. There have been a number of hypothesized explanations for an increase in risk of infection. Evidence suggests that patients with RA have immunologic abnormalities involving circulating T cells[34]. Studies have shown a decline in the number and function of natural killer cells and T-suppressor cells[35,36]. Immobility, extraarticular manifestations such as lung disease, and comorbidities may also be important causes of this increased risk.

Table 5. Comparison of controls and cases of hospitalized infection in patients with RA. Data are n (%) or mean ± SD.

Characteristic	Cases, n = 1,993	Controls, n = 9,965
Female	1,482 (74.4)	7,567 (75.9)
Age at index date, yrs	55.9 ± 13.4	50.8 ± 11.4
Followup, mo	16.3 ± 13.6	16.3 ± 13.6
Comorbid conditions		
Diabetes	438 (22.0)	1,090 (10.9)
Chronic lung disease	500 (25.1)	1,102 (11.1)
Cancer	369 (18.5)	793 (8.0)
Organic brain disease	74 (3.7)	118 (1.2)
Current NSAID/COX-2 selective inhibitor use	439 (22.0)	2,333 (23.4)
Orthopedic procedure	40 (2.0)	75 (0.8)
Seen by a rheumatologist	1,383 (69.4)	7,034 (70.6)
No. of hospitalizations between cohort entry and the index date		
0	1,223 (61.4)	8,906 (89.4)
1	452 (22.7)	751 (7.5)
2	160 (8.0)	205 (2.1)
3+	158 (7.9)	103 (1.0)

NSAID: nonsteroidal antiinflammatory drugs; COX: cyclooxygenase.

A number of studies have shown an increased risk of infection with corticosteroid use, especially at high doses, and the mechanism for this increase has been fairly well established[33,37]. Recent data suggest that even low-dose prednisone use results in an increased risk of pneumonia[21]; this is consistent with our finding that ≤ 5 mg/day was associated with increased risk of hospitalized infection. Despite case reports, traditional DMARD have not been consistently shown to be associated with an increased risk of serious infection.

We found a slight increase in the risk of hospitalized infection with biological DMARD exposure. Data on the risk of infection related to anti-TNF therapy in the literature have been mixed. Trials of biological DMARD have tended toward an increased risk of infection with these medications, but few trials showed a significantly increased risk of infection[38,39]. However, in their metaanalysis of 9 clinical trials of infliximab or adalimumab, Bongartz, *et al* demonstrated an increased risk of serious infections in the treatment arms compared to placebo (odds ratio = 2.0; 95% CI 1.3–3.1)[40]. Early cohort studies that compared patients taking biological DMARD with historical controls found varied results[41,42]. Recent data from the German biologics register suggested that the risk of infection in patients with RA is increased by treatment with anti-TNF agents[22]. An analysis of data from the Swedish biologics register found a small to moderate increase in risk of hospitalization with infection associated with TNF antagonists[23]. A 2-fold increase in risk of hospitalization with a physician-confirmed bacterial infection for TNF antagonists compared with MTX was observed in an administrative database[24]. However, recent data from the British Society for Rheumatology Biologics Register found no increased risk of

Table 6. Rate ratios for hospitalized infection in patients with RA.

Current Medication	Cases, n = 1,993: Number Exposed	Controls, n = 9,965: Number Exposed	Unadjusted Rate Ratio (95% CI)	Adjusted* Rate Ratio (95% CI)
Biological DMARD	254	1,214	1.05 (0.91–1.22)	1.21 (1.02–1.43)
Methotrexate	352	2,200	0.76 (0.67–0.86)	0.81 (0.70–0.93)
Hydroxychloroquine	172	1,207	0.68 (0.58–0.81)	0.74 (0.62–0.89)
Leflunomide	90	428	1.05 (0.84–1.33)	1.02 (0.79–1.32)
Sulfasalazine	44	328	0.66 (0.48–0.91)	0.82 (0.58–1.16)
Other traditional DMARD†	32	123	1.31 (0.88–1.94)	0.89 (0.58–1.38)
Oral corticosteroids (any)	442	1,353	1.83 (1.62–2.07)	1.92 (1.67–2.21)
Oral corticosteroids				
≤ 5 mg/day	144	633	1.28 (1.06–1.55)	1.32 (1.06–1.63)
6–10 mg/day	119	376	1.79 (1.44–2.21)	1.94 (1.53–2.46)
> 10 mg/day	179	344	2.89 (2.39–3.49)	2.98 (2.41–3.69)

* Adjusted for age, sex, other current RA medication use, diabetes, chronic lung disease, organic brain disease, cancer, orthopedic procedures, number of hospitalizations between cohort entry and the index date, and whether or not the patients saw a rheumatologist during followup. † Other traditional DMARD include tacrolimus, cyclosporine, cyclophosphamide, gold thiomalate, aurothioglucose, auranofin, and penicillamine. DMARD: disease modifying antirheumatic drugs.

overall serious infection for patients treated with anti-TNF therapies compared to conventional DMARD, although there was an increased risk of skin and soft tissue infections[25]. Data from the National Databank for the Rheumatic Diseases demonstrated no increased risk of pneumonia associated with anti-TNF therapy[21]. No increase in serious bacterial infections was observed among users of anti-TNF therapy compared with users of MTX in a study using Medicare data[26].

A strength of our study is the large, nationally representative sample of people in managed-care plans in the US. We were able to examine as outcomes overall hospitalized infection as well as specific infections in our cohort analysis, and we presented background rates including those stratified by several covariates. The database we used is comprehensive, linking physician, hospital, drug, and other medical care utilization. We expect that the data are generally complete and that they represent real-world medical care. All information on exposures, outcomes, and covariates was recorded prior to the start of our study, eliminating the possibility of biases that result from recall and reconstruction of clinical history.

Our study has several limitations. We must consider whether there was some misclassification of the inclusion of patients into the RA cohort, of the infections, or of the medication exposure. For identifying patients with RA or for classifying exposure in the analysis comparing treatments, there is little reason to believe that this type of misclassification would have been related to the exposure-outcome association; therefore, any bias would have biased our results toward the null. Sensitivity analyses that were performed to explore the effect of different definitions of exposure to medication did not result in altered conclusions. Detection bias is unlikely, since we only considered infections that are extremely serious.

Another limitation, particularly in the case-control analysis, is residual confounding by disease severity. One would expect that patients with RA receiving glucocorticoids and/or biological agents would have more severe disease than those receiving no medication or only NSAID for their disease. In addition, patients receiving biological DMARD are most likely different in many ways from those receiving traditional DMARD. Patients channeled into biological DMARD therapy may be either unresponsive or intolerant to prior therapy, thus increasing the relative risk associated with biological DMARD compared with other treatments if disease severity increases infection risk. Although we attempted to control for confounding using multiple regression with various proxies for disease severity, we lacked data on RA duration and clinical measures indicative of severity such as tender and swollen joint counts, levels of acute-phase reactants, and disability scores. Therefore, there was inevitably some degree of residual confounding and a possibility that we were not able to separate the effects of medications versus disease severity on the risk of infection; our rate ratios reported here may overestimate the true risk.

Finally, although we excluded patients with a serious infection in the 3 months prior to cohort entry, we had limited information regarding each patient's history of infectious events and whether prior events led patients to a particular therapy. Patients taking traditional DMARD are likely to have been taking those drugs for a period of time, and the patients who continued to receive therapy during this study period may have had a lower risk for adverse events such as infections related to those medications. Thus the rate of events in the traditional DMARD group may be an underestimate of what would happen in patients naive to those drugs, which may help to explain why use of MTX and hydroxychloroquine appeared to decrease the risk of hospitalized infection. Since biological DMARD were introduced just prior to the start of our study period, many of the patients taking these medications were relatively naive to these drugs; therefore, the risk of infections relative to other drugs may be inflated[43].

Our large observational study suggests that patients with RA are at increased risk of developing a hospitalized infection compared to non-RA subjects, and RA appears to confer the greatest risk increment in younger and healthier individuals. Current oral corticosteroid use was associated with approximately a 2-fold increase in risk; an increased risk was present even at low doses. Biological DMARD had a slight increase in risk, which may be due to confounding by disease severity or channeling bias, whereas current MTX and hydroxychloroquine use were associated with decreased risk. Further studies should be performed examining similar outcomes in which there is access to detailed clinical information that can be used to control for disease severity. It is also important to formally study the effect of RA and RA treatments on the risk of specific infections, as there may be significant differences in risks based on the etiology of the infections. In addition, in order to fully understand the relationship between RA and infection, it will be necessary to examine nonserious infections as well as the relationship between medication usage and the frequency of infection. Since many of the drugs used to treat RA have been associated with substantial benefit in terms of disease improvement and quality of life, any increased risk of infection must be considered in context of the benefits expected from the drugs.

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