Rheumatoid Arthritis Disease Activity and Disability Affect the Risk of Serious Infection Events in RADIUS 1

Arthur Weaver, Orrin Troum, Michele Hooper, Andrew S. Koenig, Sandeep Chaudhari, JingYuan Feng, and Deborah Wenkert

ABSTRACT. ***Objective.*** To determine whether disease activity and disability independently correlate with serious infection event (SIE) risk in a large rheumatoid arthritis (RA) cohort.

Methods. The associations between SIE and Clinical Disease Activity Index (CDAI) and Health Assessment Questionnaire-Disability Index (HAQ-DI) in the Rheumatoid Arthritis Disease-Modifying Antirheumatic Drug Intervention and Utilization Study (RADIUS 1) cohort were evaluated using the Andersen-Gill model (a proportional HR model allowing > 1 event per patient).

Results. Of 4084 patients with 347 SIE, 271 patients experienced ≥ 1 SIE. A 5-unit CDAI increase and 0.4-unit HAQ-DI increase corresponded to an increase in SIE risk with and without covariate adjustments. A 5-unit CDAI increase corresponded with a 7.7% increased SIE risk (adjusted HR 1.077, 95% CI 1.044–1.112, $p < 0.0001$) and a 0.4-unit HAQ-DI increase with a 30.1% increased risk (adjusted HR 1.301, 95% CI 1.225–1.381, $p < 0.0001$). Categorical analysis showed that more severe RA activity (even after controlling for disability) and disability were associated with an increased SIE risk.

Conclusion. Increased RA disease activity and disability were each associated with a significantly increased SIE risk in the RADIUS 1 cohort, which could not be completely accounted for by disability. (First Release June 15 2013; J Rheumatol 2013;40:1275–81; doi:10.3899/jrheum.121288)

Key Indexing Terms:
RHEUMATOID ARTHRITIS INFECTION ANTIRHEUMATIC DRUGS
DISEASE-MODIFYING ANTIRHEUMATIC DRUGS

Epidemiologic evidence suggests increased rates of serious infections in patients with rheumatoid arthritis (RA)[1,2,3]. Serious infections contribute to increased morbidity and mortality in patients with RA[4,5,6,7]. Comorbidities associated with RA such as pulmonary and cardiovascular disease[1,2,8,9,10,11,12] as well as immunosuppression due to treatment with disease-modifying antirheumatic drugs (DMARD)[9,13,14] may increase the risk of infection. Several studies have shown that increased RA disease activity itself may also increase the risk of infection[1,2,3,8,9,11,15,16,17], often concluding that this increase in infection risk is due to the associated disability[2,9,11]. However, it is unclear whether this increased infectious risk is indeed due to a concomitant increase in disability or whether at least some of the risk is independently due to the disease activity itself. This posthoc analysis evaluated the association between DMARD, comorbidities, RA disease activity, and disability on the risk of infection in RADIUS 1 (Rheumatoid Arthritis Disease-Modifying Antirheumatic Drug Intervention and Utilization Study), a 5-year, multicenter observational study[18,19] to determine whether RA activity itself increases the risk of serious infection events (SIE).

MATERIALS AND METHODS

Study design. The methodology for RADIUS 1 has been reported[18,19]. RADIUS 1 was a prospective, multicenter observational study designed to systematically collect and document data regarding use patterns, effectiveness, and safety of DMARD treatments used in the management of RA. The RADIUS 1 cohort (n = 4968) consisted of patients with RA who required a change or addition of DMARD. They were enrolled from October 2001 through January 2003 from community-based private practices (88%), academic institutions (7%), and hospitals (5%).

The frequency and scope of clinical evaluations were performed according to the investigator's routine clinical practice rather than protocol-driven. Visits were frequent: 68.7% of patient visits were within 3 months of one another and 93.1% were within 6 months of one another. Data were entered by the site at baseline and at followup visits (for up to 5 years), and included laboratory values, information on comorbid conditions, Health Assessment Questionnaire-Disability Index (HAQ-DI)[20,21], joint counts, Physician Global Assessment (PhGA), Patient Global Assessment (PtGA), antirheumatic drug therapy, and serious adverse events. Study monitoring was performed on 96% of the sites that partici-

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Sponsored by Immunex, a wholly owned subsidiary of Amgen Inc., and by Wyeth, which was acquired by Pfizer Inc. in October 2009.

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Accepted for publication April 30, 2013.

pated in the registry and targeted site compliance, safety reporting, safety data, and concomitant medication accuracy.

Medication data were collected at the time of each visit according to patient report. Nonbiologic DMARD were classified into 2 categories based on whether they were thought to pose a significant infection risk. Nonbiologic DMARD classified as posing a significant infection risk because of immunosuppression included cyclosporine, azathioprine, leflunomide, and methotrexate (MTX). Nonbiologic DMARD classified as generally not posing a significant infection risk included D-penicillamine, gold, minocycline, sulfasalazine, and hydroxychloroquine. Patients had been assessed at baseline and at intervals deemed appropriate by their physician [mean (SD) time between visits, 2.74 (2.55) months; median (Q1, Q3), 2.07 (1.35, 3.45) months].

Comorbid conditions at baseline were classified into 2 mutually exclusive groups. Extraarticular manifestations (EAM) that might reflect underlying RA severity included systemic involvement (fever, Felty syndrome, vasculitis, Sjögren syndrome), cardiopulmonary involvement (interstitial lung disease, bronchiolitis, pleural effusion or thickening, pulmonary fibrosis, pulmonary nodules, pericarditis), cutaneous and subcutaneous involvement (ulcers, rash, nodules), ophthalmologic involvement (uveitis, iritis, scleritis, episcleritis, keratoconjunctivitis sicca syndrome), and Raynaud syndrome. Comorbid conditions that were classified as "other comorbidities" were those that might confer additional SIE risk without necessarily reflecting RA severity and included chronic liver disease, congestive heart failure, renal disease, ischemic heart disease, and deep vein thrombosis. Diabetes would not be expected to influence the model because too few patients were diabetic (n = 46). Asthma and chronic obstructive pulmonary disease (COPD) were classified in a separate, nonmutually exclusive category of comorbid conditions.

Patients. Patients enrolled in RADIUS 1 were ≥ 18 years of age, had RA (per 1987 American Rheumatism Association RA criteria), and required an addition or a switch to a new biologic or nonbiologic DMARD. All RADIUS 1 patients who received ≥ 1 dose of a biologic or nonbiologic DMARD and for whom an informed consent form was verified were included in this analysis (n = 4084). Patients were excluded from any site closed for significant clinical practice violations or for whom informed consent could not be verified. Only visits involving observed data were included in the analysis. Only SIE for which concurrent treatment(s) could be verified were included. Records in which the observed treatment period was only 1 day were excluded. Multiple SIE that occurred on the same day for a given patient were counted as a single SIE.

Assessments. An infectious adverse event was defined as serious if it met any criteria consistent with the US Food and Drug Administration's definition of a serious adverse event: fatal, life-threatening, requiring inpatient hospitalization or prolongation of existing hospitalization, or persistent or significant disability or congenital anomaly[22]. Patients had been assessed using the HAQ-DI[20,21] and the Clinical Disease Activity Index (CDAI)[23]. The CDAI is a composite index based on tender/painful joint count (TJC28), swollen joint count (SJC28), PhGA, and PtGA. A prorated count was calculated for each patient based on the proportion of swollen or tender joints observed, allocated to 28 joints where at least 14 joints were assessed. In brief, if ≥ 14 joints were missing from the joint count, a prorated value was calculated by multiplying the average score from the available tender or swollen joints by 28 to provide an overall joint score. Of note, the mean (SD) and median (Q1, Q3) tender and swollen joint count values with prorated adjustments versus without prorated adjustments were similar, differing by no more than one-tenth of a joint (data not shown). Disease activity in this analysis was defined as remission (CDAI ≤ 2.8), low (CDAI > 2.8 to 10.0), moderate (CDAI > 10 to 22), or high (CDAI > 22)[23]. HAQ-DI scores were classified as normal (< 0.5), mild to moderate (0.5 to 1.0), moderate to severe (> 1.0 to 2.0), and severe (> 2.0 to 3.0)[20].

Statistical analysis. The associations between disease measures (CDAI, HAQ-DI) and serious infections were assessed using the Andersen-Gill model[24]. A Cox proportional hazards model allows estimation of risk associated with an event. The Andersen-Gill model is an extension of the Cox proportional hazards model in that it allows the estimation of risk associated with events that occur multiple times per patient. The treatment (including corticosteroid dose) and disease activity as measured by CDAI and HAQ-DI were included in the model as time-dependent variables. All other covariates were defined at the baseline visit and were not changed during followup.

The final set of covariates included in the model were the result of assessing local tests of variables estimates ($\alpha = 0.10$ for inclusion or exclusion from the final model) among those deemed clinically important by the study team. Rheumatoid factor (RF), EAM, sex, and solid tumor/lymphoma were not included as possible covariates in the final analyses after they were found to be not statistically significant ($p > 0.10$). Although EAM may be closely associated with disease activity, we discovered no significant difference in the results when treating or not treating this variable as a possible covariate for modeling purposes (data not shown); therefore, we left EAM in for our reported analyses. For continuous variable analysis, CDAI was analyzed in 5-unit increments and HAQ-DI in 0.4-unit increments (rather than 1-unit changes), with any reported change in risk therefore representing a 5-unit change in CDAI[9] or 0.4-unit change in HAQ-DI[25]. Although a 0.22-unit change is often used to reflect a minimal clinically important difference (MCID) in HAQ-DI, this value will vary by clinical setting, study type, and other factors[25,26,27,28]. Therefore, our choice (0.4 units) includes the MCID for HAQ-DI plus some margin.

Covariates. The final models from which the adjusted HR were calculated included the following covariates: (1) disease duration; (2) age at disease onset ≥ 65 years; (3) comorbid asthma or COPD; (4) EAM; (5) comorbid conditions; (6) oral corticosteroid dose < 5 mg/day; (7) oral corticosteroid dose 5 to 10 mg/day; (8) oral corticosteroid dose ≥ 10 mg/day; (9) nonbiologic DMARD; (10) biologic DMARD; and (11) previous hospitalization due to infection. A series of 6 models were fitted using these covariates. The first 4 were CDAI (5 units) only, HAQ-DI (0.4 unit) only, CDAI (ordinal) only, and HAQ-DI (ordinal) only. In addition, although both CDAI and to some degree HAQ-DI reflect RA disease activity, we analyzed each controlling for the other to determine whether the effect of disease activity on disability confers all the increase in risk of infection. Thus, 2 additional models were used: CDAI (5 unit) and HAQ-DI (0.4 unit), and CDAI (ordinal) and HAQ-DI (ordinal). The time-dependent variables were biologic and nonbiologic treatment, CDAI, HAQ-DI, and corticosteroid dose. Patients entered the model at baseline and exited at the end of the study, which was, by protocol, 5 years. For patients who exited the study before 5 years, the time of observation was the date of study entry to the date of study exit. Observed data were used to fit the models. Observations with missing data were excluded from the analysis. All analyses were performed using the SAS statistical software package version 9.2 (SAS Institute).

RESULTS

Patients. In RADIUS 1, 4968 patients were enrolled across 387 sites between October 2001 and January 2003. A total of 884 patients were excluded from this analysis because of protocol violations or being in the study for only 1 day. The remaining 4084 RADIUS 1 patients who received ≥ 1 dose of a biologic or nonbiologic DMARD qualified for inclusion in this analysis of serious infection risk. Of the 4084 patients, 50% completed the study, 20% were lost to followup, 9% withdrew after a patient request, 5% withdrew because of patient relocation, 4% died, 1% discontinued because of adverse events, and 10% left for other, undefined reasons. The mean (SD) duration of followup was 3.17 (1.78) years for RADIUS 1 patients in our analysis (median 4.04 years).

Demographic data are provided in Table 1. The majority

of patients were white (81%) and the majority were women (76%). Mean (SD) age was 55.74 (13.57) years (median 55.59 years). A total of 587 (14.4%) patients were at least 65 years old at disease onset. Twenty-two percent had EAM classified as associated with RA, 5% of patients had comorbidities that were classified as not associated with RA, and 11% had comorbid asthma or COPD. A total of 1585 (39%) patients received ≥ 1 dose of a biologic DMARD. Of the 4972 biologic treatments used by these patients, infliximab (43%), etanercept (32%), and adalimumab (19%) were the most frequently used agents, followed by anakinra (15%), abatacept (2%), and rituximab (1%). Eighty percent received a nonbiologic DMARD classified as posing an infection risk, and 36% received a nonbiologic DMARD classified as not posing a significant infection risk. At baseline, prednisone was used by 56% of patients, and 24% of patients received > 10 mg/day of oral prednisone or equivalent. At baseline, 2759 (67.6%) patients were receiving MTX, and the mean (SD) and median weekly doses of MTX were 12.46 (5.46) mg and 10 mg, respectively.

At baseline (Table 2), patients had a mean CDAI of 35.72 (median 34.00) and a mean HAQ-DI of 1.29 (median 1.25), with a mean erythrocyte sedimentation rate (ESR) of 36.31 mm/h (median 30.00 mm/h). The mean disease duration was 7.33 years (median 3.54 years). The mean SJC28 and TJC28 (both prorated) were 7.87 and 8.48 (median 6.00 for both), respectively. The mean PhGA and PtGA were 4.37 and 4.82 (median 4.00 and 5.00), respectively. Determination of CDAI at baseline indicated that 3% of patients were in remission (CDAI ≤ 2.8), 18% had low disease activity (> 2.8 to 10.0), 30% had moderate disease activity (> 10–22), and 49% had high disease activity (> 22). For HAQ-DI at baseline, 23% of patients were classified as normal (HAQ-DI < 0.5), 26% were in the low range (0.5–1.0), 41% were in the moderate range (> 1.0–2.0), and 10% were in the severe range (> 2.0).

Table 1. Patient demographics.

Characteristic	N	n (%)
Female	4084	3114 (76.25)
White	4084	3310 (81.05)
Age at disease onset ≥ 65 yrs	4083	587 (14.38)
Rheumatoid factor-positive	3779	2957 (78.25)
Comorbid asthma or COPD	4084	455 (11.14)
Extraarticular manifestations (classified as associated with RA*)	4084	907 (22.21)
Ischemic heart disease	4084	171 (4.19)
Comorbid conditions classified as not associated with RA†	4084	196 (4.80)
Prednisone use	4084	2306 (56.46)
Biologic DMARD	4084	1585 (38.81)
Nonbiologic DMARD classified as posing a significant infection risk	4084	3281 (80.34)
Nonbiologic DMARD classified as not posing a significant infection risk	4084	1488 (36.43)
Received > 10 mg/day oral prednisone or equivalent	4084	975 (23.87)

* Fever, Felty syndrome, vasculitis, Sjögren syndrome, interstitial lung disease, bronchiolitis, pleural effusion or thickening, pulmonary fibrosis, pulmonary nodules, ulcers, rash, nodules, uveitis, iritis, scleritis, episcleritis, keratoconjunctivitis sicca, Raynaud syndrome, and pericarditis. † Chronic liver disease, congestive heart failure, ischemic heart disease, renal disease, and deep vein thrombosis. COPD: chronic obstructive pulmonary disease; DMARD: disease-modifying antirheumatic drug; RA: rheumatoid arthritis.

Table 2. Baseline clinical measures.

Clinical Measures	N	Mean (SD)	Median (Q1, Q3)
CDAI	3970	35.72 (16.65)	34.00 (23.00, 48.00)
HAQ-DI	4080	1.29 (0.70)	1.25 (0.75, 1.88)
Disease duration, yrs	4083	7.33 (9.12)	3.54 (0.53, 11.22)
28 swollen joint count, prorated	4017	7.87 (7.19)	6.00 (2.00, 12.00)
28 tender joint count, prorated	4016	8.48 (8.32)	6.00 (2.00, 14.00)
Erythrocyte sedimentation rate, mm/h	1640	36.31 (27.03)	30.00 (15.00, 51.00)
Physician global assessment	4078	4.37 (2.26)	4.00 (3.00, 6.00)
Patient global assessment	4042	4.82 (2.56)	5.00 (3.00, 7.00)

CDAI: Clinical Disease Activity Index; HAQ-DI: Health Assessment Questionnaire-Disability Index.

Serious infectious events. A total of 347 SIE were observed. At least 1 SIE was experienced by 271 patients, of whom 33 had 2 SIE, 7 had 3 SIE, 7 had 4 SIE, and 1 had 9 SIE. The incidence rate was estimated to be 2.679 (95% CI 2.404–2.976) SIE per 100 patient-years. Among patients who were at least 65 years old at disease diagnosis (onset), 9.8% had SIE. SIE occurring with > 2% incidence included 80 (23.1% of SIE) events of pneumonia, 19 (5.5%) cellulitis, 16 (4.6%) sepsis, 10 (2.9%) urosepsis, 9 (2.6%) diverticulitis, and 9 (2.6%) pyelonephritis. In our analysis of SIE, there were 2 (0.6%) cases of herpes zoster and no cases of tuberculosis. The mean and median times from the start of observation to development of SIE were both around 2 years (range 0.01–5.00 years). There were no fatal SIE.

The overall correlation between HAQ-DI and CDAI was 0.4610. Because patients with higher CDAI are exposed to different medications and may have other SIE risk factors that are not directly related to their disease activity, these factors were evaluated to determine whether they were correlated with an increased SIE risk in this population (Table 2). Sex, RF status, age at disease onset, use of non-biologic or biologic DMARD, and leukemia/lymphoma or solid tumor showed no statistically significant correlation with SIE ($p > 0.10$). Although EAM may be closely associated with disease activity, we discovered no significant difference in the results when treating or not treating this variable as a possible covariate for modeling purposes (data not shown); therefore, we left EAM in for our reported analyses. However, disease duration, asthma or COPD,

comorbid conditions (such as chronic liver disease, congestive heart failure, ischemic heart disease, renal disease, and deep vein thrombosis), corticosteroid use, and previous hospitalization as a result of infection (before the study baseline visit date) were, as expected, each associated with higher risk of SIE, and they were therefore included as covariates in the final models. The final models from which the adjusted HR were calculated were fitted using the procedures described.

Unadjusted models A and B. Those who had a 5-unit higher CDAI had an 11.9% increased unadjusted risk of SIE (unadjusted HR 1.119, 95% CI 1.087–1.152, p < 0.0001). After covariate adjustment, for every 5-unit higher CDAI, a 7.7% increased risk of SIE remained (adjusted HR model A, 1.077; 95% CI 1.044–1.112; p < 0.0001). A 0.4-unit change in HAQ-DI resulted in a 43.4% increased unadjusted risk of SIE (unadjusted HR 1.434, 95% CI 1.356–1.516, p < 0.0001) and a 30.1% increased adjusted risk of SIE (adjusted HR model B, 1.301; 95% CI 1.225–1.381; p < 0.0001).

Adjusted models C and D. Table 3 provides SIE hazard estimates at different severity levels of disease using CDAI or HAQ-DI as the measure of disease activity. Holding constant the other factors that may contribute to the risk of SIE, the risk was shown to increase 2.7-fold for low disease activity as measured by CDAI (adjusted HR model C, 2.715; 95% CI 1.178–6.258; p = 0.0191), to nearly 4.3-fold for moderate disease activity (adjusted HR model C, 4.261; 95% CI 1.870–9.710; p = 0.0006), to 4.8-fold for high disease activity (adjusted HR model C, 4.800; 95% CI 2.110–10.924; p = 0.0002). The risk was shown to increase from 1.7-fold for HAQ-DI scores in the lowest disease activity category (adjusted HR model D, 1.700; 95% CI 1.119–2.584; p = 0.0129), to 2.5-fold for moderate to severe disease activity (adjusted HR model D, 2.508; 95% CI 1.731–3.633; p < 0.0001), to nearly 4.5-fold for HAQ-DI scores in the highest disease activity category (adjusted HR model D, 4.462; 95% CI 2.990–6.657; p < 0.0001).

Adjusted models E and F. In this model (Table 4), a 0.4-unit change in HAQ-DI (adjusted for all covariates including CDAI) resulted in a 28.5% increase in risk (adjusted HR model E, 1.285; 95% CI 1.204–1.372; p < 0.0001); a 5-unit change in CDAI (adjusted for all covariates including HAQ-DI) resulted in a 2.0% increase in risk (adjusted HR model E, 1.020; 95% CI 0.984–1.056; p = 0.2803). There was, however, a significant effect of CDAI controlled for HAQ-DI at moderate and high CDAI values in the ordinal model (model F; Table 5).

DISCUSSION

In our analysis of the RADIUS 1 cohort, we found a correlation between increased disease activity or disability (assessed by CDAI and HAQ-DI, respectively) and an increased risk of SIE. For example, compared with patients

Table 3. SIE hazard estimates at different severity levels of disease controlling for all other variables, using CDAI or HAQ-DI as the measure of disease activity.

Covariate	CDAI		HAQ-DI	
	Adjusted HR (95% CI)	p	Adjusted HR (95% CI)	p
CDAI				
Low disease activity	2.715 (1.178–6.258)	0.0191	NA	NA
Moderate disease activity	4.261 (1.870–9.710)	0.0006	NA	NA
High disease activity	4.800 (2.110–10.924)	0.0002	NA	NA
HAQ-DI				
0.5–1.0	NA	NA	1.700 (1.119–2.584)	0.0129
> 1.0–2.0	NA	NA	2.508 (1.731–3.633)	< 0.0001
> 2.0–3.0	NA	NA	4.462 (2.990–6.657)	< 0.0001
Disease duration	1.019 (1.009–1.030)	0.0003	1.014 (1.003–1.024)	0.0112
Age at disease onset ≥ 65 yrs	1.289 (0.930–1.785)	0.1269	1.217 (0.879–1.685)	0.2364
Comorbid asthma or COPD	1.925 (1.479–2.505)	< 0.0001	1.767 (1.358–2.298)	< 0.0001
Extraarticular manifestations*	1.464 (1.147–1.868)	0.0022	1.444 (1.132–1.841)	0.0031
Comorbid conditions†	2.388 (1.662–3.430)	< 0.0001	2.395 (1.671–3.434)	< 0.0001
Oral corticosteroid dose				
< 5 mg/day	1.599 (1.082–2.362)	0.0184	1.680 (1.142–2.471)	0.0084
5–10 mg/day	1.688 (1.277–2.232)	0.0002	1.655 (1.252–2.188)	0.0004
≥ 10 mg/day	2.835 (2.146–3.746)	< 0.0001	2.702 (2.047–3.565)	< 0.0001
Nonbiologic DMARD††	1.071 (0.810–1.417)	0.6301	1.095 (0.828–1.448)	0.5258
Nonbiologic DMARD#	0.912 (0.716–1.162)	0.4545	0.947 (0.744–1.205)	0.6589
Biologic DMARD	1.125 (0.897–1.411)	0.3070	1.080 (0.861–1.354)	0.5057
Previous hospitalization due to infection	2.284 (1.661–3.138)	< 0.0001	2.044 (1.486–2.811)	< 0.0001

* Classified as associated with RA. † Classified as not associated with RA. †† Classified as posing a significant infection risk. # Classified as not posing a significant infection risk. CDAI: Clinical Disease Activity Index; COPD: chronic obstructive pulmonary disease; DMARD: disease-modifying antirheumatic drug; HAQ-DI: Health Assessment Questionnaire-Disability Index; NA: not applicable; RA: rheumatoid arthritis; SIE: serious infection event.

Table 4. SIE hazard estimates controlling for all other variables, using CDAI and HAQ-DI as measures of disease activity.

Covariate	Adjusted HR (95% CI)	p
CDAI, 5 unit	1.020 (0.984–1.056)	0.2803
HAQ-DI, 0.4 unit	1.285 (1.204–1.372)	< 0.0001
Disease duration	1.012 (1.002–1.023)	0.0245
Age at disease onset ≥ 65 yrs	1.244 (0.897–1.725)	0.1900
Comorbid asthma or COPD	1.741 (1.336–2.268)	< 0.0001
Extraarticular manifestations*	1.423 (1.113–1.818)	0.0049
Comorbid conditions†	2.398 (1.672–3.439)	< 0.0001
Oral corticosteroid dose		
< 5 mg/day	1.653 (1.118–2.444)	0.0117
5–10 mg/day	1.598 (1.206–2.116)	0.0011
≥ 10 mg/day	2.535 (1.912–3.361)	< 0.0001
Nonbiologic DMARD††	1.093 (0.826–1.446)	0.5342
Nonbiologic DMARD#	0.949 (0.745–1.209)	0.6731
Biologic DMARD	1.083 (0.863–1.358)	0.4912
Previous hospitalization due to infection	1.977 (1.433–2.727)	< 0.0001

* Classified as associated with RA. † Classified as not associated with RA. †† Classified as posing a significant infection risk. # Classified as not posing a significant infection risk. CDAI: Clinical Disease Activity Index; COPD: chronic obstructive pulmonary disease; DMARD: disease-modifying antirheumatic drug; HAQ-DI: Health Assessment Questionnaire-Disability Index; RA: rheumatoid arthritis; SIE: serious infection event.

Table 5. SIE hazard estimates at different severity levels of disease controlling for all other variables, using CDIA and HAQ-DI as measures of disease activity.

Covariate	Adjusted HR (95% CI)	p
CDAI		
Low disease activity	2.093 (0.898–4.878)	0.0869
Moderate disease activity	2.740 (1.177–6.380)	0.0194
High disease activity	2.685 (1.147–6.285)	0.0229
HAQ-DI		
0.5–1.0	1.511 (0.983–2.322)	0.0598
> 1.0–2.0	2.066 (1.392–3.065)	0.0003
> 2.0–3.0	3.638 (2.366–5.594)	< 0.0001
Disease duration	1.013 (1.003–1.024)	0.0140
Age at disease onset ≥ 65 yrs	1.253 (0.904–1.736)	0.1759
Comorbid asthma or COPD	1.779 (1.365–2.317)	< 0.0001
Extraarticular manifestations*	1.435 (1.124–1.833)	0.0038
Comorbid conditions†	2.378 (1.658–3.413)	< 0.0001
Oral corticosteroid dose		
< 5 mg/day	1.634 (1.105–2.415)	0.0138
5–10 mg/day	1.615 (1.220–2.138)	0.0008
≥ 10 mg/day	2.626 (1.984–3.476)	< 0.0001
Nonbiologic DMARD††	1.091 (0.824–1.443)	0.5443
Nonbiologic DMARD#	0.932 (0.731–1.187)	0.5673
Biologic DMARD	1.080 (0.861–1.356)	0.5043
Previous hospitalization due to infection	2.049 (1.488–2.823)	< 0.0001

* Classified as associated with RA. † Classified as not associated with RA. †† Classified as posing a significant infection risk. # Classified as not posing a significant infection risk. CDAI: Clinical Disease Activity Index; COPD: chronic obstructive pulmonary disease; DMARD: disease-modifying antirheumatic drug; HAQ-DI: Health Assessment Questionnaire-Disability Index; RA: rheumatoid arthritis; SIE: serious infection event.

who were in remission, patients with CDAI of mild, moderate, or severe disease activity experienced a 2.7-fold, 4.3-fold, or 4.8-fold increase in SIE risk, respectively. After adjustment for disease duration, comorbidities, oral corticosteroid dose, and previous hospitalization due to infection, the association between increased risk of SIE and disease activity was still statistically significant even when controlled for disability. The same was true for disability adjusted in the same way and controlled for as disease activity.

Although scores for the disease activity and disability measures used in our analysis (CDAI and HAQ-DI) vary with active disease, they do not do so in parallel. Some studies have proposed that the disability associated with active RA may account for the increased incidence of SIE related to RA disease activity[2,29,30]; therefore, we attempted to address this possibility by controlling each measure for the other. Consistent with the concept that the disability that is a feature of increased disease activity confers at least some of the SIE risk, HAQ-DI controlled for CDAI was still statistically significantly correlated with an increase in SIE risk in both the continuous and in the 2 higher ordinal categories of HAQ-DI. However, disease activity also seems to have an influence on SIE risk independent of disability. This is supported by a statistically significant association between CDAI and SIE that remained after controlling for HAQ-DI in the 2 higher ordinal CDAI disease activity categories. A sensitivity analysis was performed using a proportional hazards model with time-varying covariates but evaluating only the first SIE event for each patient. The overall conclusions were the same, with variable estimates being similar across all models tested. These novel findings suggest that disease activity and disability both contribute to an increased risk for serious infection.

Other evaluations of SIE in RA populations have found many of the same nondisease activity–related "predictors of infection" as we found, such as duration of RA[9,10], history of infection[8,9], glucocorticoids[2,8], disability status[9,11], and comorbidities (e.g., pulmonary and cardiovascular disease)[1,2,8,9,10,11]. Additional predictors found in other registries[9,10,11] or databases[1,2,8] that either were not significant or were not evaluated in our registry have included age, sex, socioeconomic status, and health insurance. The associations found in previous evaluations (along with differences in populations) were used for modeling our analyses. This, along with differences in the statistical methods used, may explain some of the differences in risk.

Many medications used in the treatment of RA dampen the immune response in an attempt to diminish the destructive consequences of the disease. Immunosuppressive agents, by definition, can increase the risk of infection and reportedly carry an increased risk of SIE in the RA population[10,31,32]; however, other variables appear to

contribute to the risk of infection, as demonstrated by one analysis in which SIE risk did not increase irrespective of the immunosuppressive activity of nonbiologic DMARD therapy[8]. Interestingly, in that retrospective study using administrative data, use of a DMARD (immunosuppressive or nonimmunosuppressive) in conjunction with corticosteroids was associated with a 14% SIE reduction ($p = 0.003$ vs corticosteroids alone) and among corticosteroid nonusers, an 8% to 11% reduction in mild infections ($p < 0.0001$). Although some other studies find a DMARD-associated increased SIE risk, most also implicate the underlying disease. It remains unclear how much of the risk is due to the underlying disease and whether this risk is increased with increased disease activity[29,30,33,34].

Studies have shown that disease activity and disability increase infection risk in patients with RA. A multivariate analysis of SIE in RA in the Rochester Epidemiology Project identified 5 "disease-related" variables (EAM, RF, rheumatoid nodules, functional capacity, and ESR), each associated with an increased risk of infection[2]. The evaluation of additional robust databases also supports an association between SIE and RA disease activity[9,11]. The study of 6247 patients in the CORRONA database reported that each 5-unit increase in CDAI score in patients with CDAI < 10 (mild disease activity) increased the risk of outpatient infections by 14% and the risk of infections requiring hospitalization by 56%[9]. HAQ-DI scores from the CORRONA[9] (univariate but not multivariate) analysis as well as from the Swedish Biologics Register (ARTIS; both univariate and multivariate analysis)[35] were also significantly correlated with outpatient and hospitalized infection rates. The rate of SIE in our analysis (2.68 per 100 patient-years) fell between the values for outpatient (31.2 per 100 patient-years) and infections requiring hospitalization (0.8 per 100 patient-years) in the CORRONA study[9], as expected based on the criteria used to define infections in the 2 studies. In addition, analysis of pneumonia and HAQ, in a database of over 16,000 patients with RA, showed an association between each 1-unit increase in HAQ score and a 2-fold increased risk of hospitalized pneumonia[36]. The findings from our analysis support these results from other studies and extend these data by controlling for the disease activity and disability variables to show that each independently contributes to SIE risk.

Study limitations include short followup (average about 3.2 yrs) for a lifelong disease, a cohort of 4084 patients limiting the number of patients in each age category, the possibility that not all factors associated with SIE were captured, possible failure to enroll sicker patients or those at greatest risk of SIE in RADIUS because they may not have been thought to be good study candidates, and the exclusion of patients with active tuberculosis, hepatitis B or C or cancer. There is also the potential that the use of prorated joint counts may have altered CDAI results; however, over the course of our study, prorated mean and median joint count values did not vary significantly from the raw joint count values, indicating that there was no excess of missing joint count values that might bias results and conclusions drawn from them. In addition, based on the criteria used to define SIE, it is possible that some medically important infections that were treated on an outpatient basis may have been excluded. The authors also acknowledge the difficulty in controlling for channeling bias (patients with more severe disease have more DMARD exposure). Confounding by indication or other medications may also have had a role in the observed association between disease severity and SIE risk. Lastly, not all comorbid diseases were analyzed.

Nonetheless, our findings support the results from other studies that have assessed the effect of disease activity and disability on infection risk and extend these data by controlling for the disease activity and disability variables to show that each contributes independently to SIE risk. RADIUS 1 was an observational inception cohort of patients who had RA disease activity that required a therapeutic intervention. Although RADIUS 1 patients may not reflect the full spectrum of disease activity, duration, or severity, results obtained from this cohort may be more generalizable to practicing rheumatologists than those from a randomized controlled trial because of study size, duration, and enrollment criteria.

In the RADIUS 1 cohort, we identified and controlled for comorbidities conferring increased SIE risk, controlled for use of immunosuppressive agents, and showed that increased RA disease activity as measured by CDAI, disability as measured by HAQ-DI, HAQ-DI controlled for CDAI, and CDAI controlled for HAQ-DI, each significantly raised the risk of SIE. Thus, the increased infectious risk conferred by increased disease activity was not entirely explained by disability. This highlights the difficulty facing the clinician in differentiating the risk conferred by comorbidities, by immunosuppressive agents, and by disability, from that conferred by the underlying disease activity.

ACKNOWLEDGMENT

Dikran Toroser (Amgen Inc.) and Rick Davis (Complete Healthcare Communications, Inc., on behalf of Amgen) provided assistance in drafting this report.

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