

# Impact of Sustained Remission on the Risk of Serious Infection in Patients With Rheumatoid Arthritis

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**Objective.** This retrospective analysis examined how sustained remission impacted risk of serious infections in patients with rheumatoid arthritis (RA) enrolled in a clinical registry.

**Methods.** Inclusion criteria included RA diagnosis, age  $\geq 18$  years, and  $\geq 2$  Clinical Disease Activity Index (CDAI) scores followed by a followup visit. Index date was the second of 2 visits in which a patient had sustained remission (CDAI  $\leq 2.8$ ), low disease activity (LDA;  $2.8 < \text{CDAI} \leq 10$ ), or moderate-to-high disease activity (MHDA; CDAI  $> 10$ ). Followup extended from the index date until first serious infection (requiring intravenous antibiotics or hospitalization) or last followup visit. The crude incidence rate (IR) per 100 patient-years for serious infections was calculated for the sustained remission, LDA, and MHDA groups. The multivariable-adjusted incidence rate ratio (IRR) (adjusted for age, sex, and prednisone dose) compared serious infection rates across disease activity groups.

**Results.** Most patients were female ( $>70\%$ ); mean age was approximately 60 years. The crude IR (95% confidence interval [95% CI]) per 100 patient-years for serious infections was 1.03 (0.85–1.26) in the sustained remission group ( $n = 3,355$ ), 1.92 (1.68–2.19) in the sustained LDA group ( $n = 3,912$ ), and 2.51 (2.23–2.82) in the sustained MHDA group ( $n = 5,062$ ). Compared to sustained remission, the serious infection rate was higher in sustained LDA (adjusted IRR 1.69 [95% CI 1.32–2.15]). Compared to sustained LDA, the serious infection rate was higher in sustained MHDA (adjusted IRR 1.30 [95% CI 1.09–1.56]).

**Conclusion.** In this study, lower RA disease activity was associated with lower serious infection rates. This finding may motivate patients and health care providers to strive for remission rather than only LDA.

## INTRODUCTION

Patients with rheumatoid arthritis (RA) are at an increased risk for infection compared with subjects without RA (1). This finding has been observed to extend to an increased risk of serious infections that require hospitalization (2). Infection risk in patients with RA may be also affected by medications used, comorbidities (e.g., diabetes mellitus),

health habits (e.g., smoking), and other factors (3,4). Compared with the general population, patients with RA have increased mortality, which may be partly due to the higher infection rate associated with RA (5–10). Infections could also limit the type of treatment a patient with RA is subsequently prescribed by a physician (11).

The relationship between the level of RA disease activity and the risk of infection has not been extensively studied.

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## Significance & Innovations

- In this retrospective analysis of data from a rheumatoid arthritis (RA) registry, the adjusted rate of serious infections was 69% higher in patients in sustained low disease activity (LDA) compared with patients in sustained remission.
- In absolute terms, remission and LDA were associated with a lower rate of serious infections (1–2 cases per 100 patient-years) compared to patients in moderate or high disease activity.
- The goal of attaining the lowest possible RA disease activity may lead to reduced risk for serious infections.

One study found that higher scores for the Disease Activity Score based on 28 joints were associated with serious infections (12). Another study found that for patients in low disease activity (LDA), higher levels of disease activity (within the LDA category) were associated with an increase in outpatient infections (3). Though RA remission as opposed to only LDA is the desired goal of RA therapy (13), the potential benefit of a lower infection rate for patients in remission compared to LDA has not been examined.

By retrospectively analyzing data from a cohort of patients with RA enrolled in a clinical registry in the US, the present study compared the incidence rate (IR) of serious infections in patients achieving sustained remission with the IR in patients in sustained LDA. As a further comparator, the incidence of serious infections was examined between patients in LDA and patients in moderate-to-high disease activity (MHDA).

## PATIENTS AND METHODS

**Study design and patient population.** This was a retrospective analysis of data from a cohort of patients with RA enrolled in the CORRONA RA registry. This registry collects longitudinal, real-world data from patients ages  $\geq 18$  years diagnosed with RA. CORRONA data collection methods have been fully described (14). The CORRONA site network includes 165 private and academic practices across 40 states in the US. The data collected included potential confounders such as demographic characteristics (race, education, weight, body mass index, smoking status, work status, and insurance type), RA characteristics (duration of RA, rheumatoid factor positivity, cyclic citrullinated peptide antibody status, pain, morning stiffness, and duration of morning stiffness), non-RA clinical characteristics (history of cancer/malignancy, cardiovascular disease, and nonserious infection), and treatments for RA (prior number of conventional disease-modifying antirheumatic drugs, prior number of tumor necrosis factor inhibitors [TNFi] and non-TNFi biologic medications, and prednisone dose). At each CORRONA registry visit, data were recorded on disease severity and activity, medications, adverse events, quality of life, laboratory and imaging results, and sociodemographic

information. The CORRONA registry has standard operating procedures to monitor, perform edit and logic checks, and make corrections to data if needed. Data at each site were regularly reviewed by the registry for completeness and internal consistency.

The study population consisted of patients enrolled in the CORRONA registry between March 1, 2003 and August 30, 2015. Data on diagnosis of infections were routinely captured during regularly scheduled CORRONA visits. Serious infections were defined as requiring either hospitalization or treatment with intravenous (IV) antibiotics. Patient inclusion criteria included diagnosis of RA, age  $\geq 18$  years, and at least 2 Clinical Disease Activity Index (CDAI) scores. The index date (baseline) was defined as the second of 2 consecutive visits in which a patient had sustained remission, LDA, or MHDA (defined below in the subsection on disease activity); patients had to have at least 1 followup visit after the index date. Patients with infections between index date and initial visit were included. Patients were excluded if they had a history of serious infections or malignancy during the baseline period (defined as 6 months prior to the index date). Followup extended from the index date until the earliest of the following dates: 1) first serious infection, 2) last CORRONA visit, or 3) incident malignancy.

**RA disease activity.** Disease activity was determined at the index visit and thereafter using the CDAI (15). The CDAI is commonly used in the US in settings when acute-phase reactant (e.g., C-reactive protein) measurements are not available in real time (15). Remission was defined as CDAI  $\leq 2.8$ , LDA as  $2.8 < \text{CDAI} \leq 10$ , moderate disease activity as  $10 < \text{CDAI} \leq 22$ , and high disease activity as CDAI  $> 22$ . Since a focus of this study was to examine remission versus LDA, the moderate disease activity and high disease activity groups were combined into 1 MHDA group (CDAI  $> 10$ ). Sustained remission was defined by 2 consecutive visits in which the patient was in remission preceded by a visit where the patient was not in remission. This definition, therefore, describes patients who were newly attaining remission. Patients were defined in the sustained remission exposure category after the start of followup based on their mean disease activity level (averaged over time from the index date). Mean disease activity level was estimated as time-updating and was calculated using the area under the curve method based on the trapezoidal rule (16). This procedure allowed for small deviations in the disease activity level. For example, if a patient had CDAI values of 2.0, 1.5, and 3.2 on equally spaced consecutive visits, the patient could remain in the sustained remission category since the mean CDAI was below 2.8. Similar definitions and requirements for sustained disease activity for 2 visits were used for the sustained LDA and MHDA categories. For ease of interpretation, if a patient could have contributed person-time to both the sustained remission and sustained LDA categories, the patient was only included in the sustained remission category; this categorization resulted in 196 patients being excluded from the LDA group with total person-years of 408.5. If a patient belonged to both the sustained LDA category and the sustained MHDA category, the patient was only included in the sustained LDA category;

this categorization resulted in 423 patients being excluded from the MHDA group with total person-years of 1,392.0.

A sensitivity analysis was conducted in which patients were reclassified by requiring them to continue to meet the disease activity criteria of their initially assigned disease activity category throughout followup. This alternative exposure classification was more stringent and, therefore, did not

permit slight deviations in disease activity. Patients were defined as “persistent” in their disease state if they remained in remission or in LDA throughout followup according to this more stringent definition. Of note, the persistent-remission cohort was defined as patients in remission after baseline until the occurrence of serious infection, last visit, or loss of remission. This cohort was a subset of the patients in

**Table 1. Baseline demographics and clinical characteristics\***

	<b>Sustained remission, n = 3,355</b>	<b>Sustained LDA, n = 3,912</b>	<b>Sustained MHDA, n = 5,062</b>	<b>LDA vs. remission, P</b>	<b>MHDA vs. LDA, P</b>
Sex, no.†	3,346	3,907	5,047		
Female, no. (%)	2,391 (71.5)	3,028 (77.5)	3,980 (78.9)	< 0.001	0.123
Age in years, no.	3,344	3,898	5,036		
Mean ± SD	59.4 ± 13.5	61.0 ± 12.9	60.8 ± 13.0	0.007	0.297
Race, no.	3,320	3,866	4,987	0.216	0.012
White, no. (%)	3,034 (91.4)	3,512 (90.8)	4,461 (89.5)		
African American, no. (%)	158 (4.8)	216 (5.6)	341 (6.8)		
Asian, no. (%)	61 (1.8)	55 (1.4)	52 (1.0)		
Other, no. (%)	67 (2)	83 (2.1)	133 (2.7)		
RA duration, no.	3,308	3,877	5,002		
Mean ± SD	9.9 ± 8.7	12.2 ± 10.2	12.8 ± 10.4	< 0.001	0.165
CDAI, no.	3,355	3,912	5,062		
Mean ± SD	1.1 ± 0.8	6.2 ± 2.0	20.6 ± 9.8	–	–
RF/CCP status, no.	2,276	2,554	3,175		
Positive, no. (%)	1,770 (77.8)	2,001 (78.3)	2,413 (76.0)	0.627	0.086
Comorbid conditions, no.	3,355	3,912	5,062		
History of malignancy, no. (%)	308 (9.2)	380 (9.7)	467 (9.2)	0.439	0.433
History of CVD, no. (%)	125 (3.7)	203 (5.2)	317 (6.3)	0.003	0.031
History of nonserious infection, no. (%)	554 (16.5)	651 (16.6)	888 (17.5)	0.883	0.261
History of diabetes mellitus, no. (%)	208 (6.2)	313 (8.0)	492 (9.7)	0.003	0.005
History of COPD, no.‡	2,545	2,695	3,421		
No. (%)	25 (1.0)	51 (1.9)	51 (1.5)	0.006	0.223
Smoking status, no.	3,340	3,902	5,032	< 0.001	0.084
Never smoker, no. (%)	1,883 (56.4)	2,063 (52.9)	2,582 (51.3)		
Previous smoker, no. (%)	1,084 (32.5)	1,224 (31.4)	1,570 (31.2)		
Current smoker, no. (%)	373 (11.2)	615 (15.8)	880 (17.5)		
Current DMARDs, no.	3,355	3,912	5,062	< 0.001§	< 0.001§
TNFi monotherapy, no. (%)	389 (11.6)	356 (9.1)	507 (10.0)		
MTX monotherapy, no. (%)	835 (24.9)	817 (20.9)	968 (19.1)		
Other monotherapy, no. (%)	172 (5.1)	194 (5.0)	449 (8.9)		
Any combination therapy, no. (%)	1,554 (46.3)	2,128 (54.4)	2,452 (48.4)		
Not on therapy, no. (%)	405 (12.1)	417 (10.7)	686 (13.6)		
Current prednisone use, no. (%)	294 (8.8)	668 (17.1)	959 (18.9)	< 0.001	< 0.001
Dose <5 mg, no. (%)	144 (4.3)	226 (5.8)	182 (3.6)		
Dose ≥5 mg, no. (%)	150 (4.5)	442 (11.3)	777 (15.3)		
Number of prior cDMARDs, no.	3,355	3,912	5,062		
Mean ± SD	0.7 ± 0.9	0.9 ± 1.1	1.1 ± 1.2	< 0.001	< 0.001
Prior medications, no.	3,355	3,912	5,062		
cDMARD, no. (%)	1,532 (45.7)	2,140 (54.7)	3,024 (59.7)	< 0.001	< 0.001
TNFi, no. (%)	1,800 (53.7)	2,494 (63.8)	3,355 (66.3)	< 0.001	< 0.001
Non-TNFi bDMARD, no. (%)	303 (9.0)	626 (16.0)	906 (17.9)	< 0.001	< 0.001
bDMARD/tsDMARD, no. (%)	1,873 (55.8)	2,597 (66.4)	3,482 (68.8)	< 0.001	< 0.001
NSAID, no. (%)	1,670 (49.8)	1,991 (50.9)	2,472 (48.8)	0.342	0.053
Opiate, no. (%)	415 (12.4)	1,172 (30.0)	1,901 (37.6)	< 0.001	< 0.001

\* LDA = low disease activity; MHDA = moderate-to-high disease activity; RA = rheumatoid arthritis; CDAI = Clinical Disease Activity Index; RF = rheumatoid factor; CCP = cyclic citrullinated peptide; CVD = cardiovascular disease; COPD = chronic obstructive pulmonary disease; DMARDs = disease-modifying antirheumatic drugs; TNFi = tumor necrosis factor inhibitor; MTX = methotrexate; cDMARDs = conventional DMARDs; bDMARD = biologic DMARD; tsDMARD = targeted synthetic DMARD; NSAID = nonsteroidal antiinflammatory drug.

† The percentage for each variable is based on nonmissing numbers.

‡ Measure not included in the CORRONA RA questionnaire until version 7 (late 2008).

§ P values based on chi-square test to compare the use of any and all current DMARDs between cohorts.

sustained remission, which was defined based on their average disease activity in remission over the followup.

**Statistical analyses.** Statistical analyses were conducted using Stata, version 13 (StataCorp LP). Categorical variables were summarized using frequency counts and percentages. Continuous variables were summarized by providing the number of observations, mean, SD, median, interquartile range (IQR), 25th and 75th percentiles, and 95% confidence intervals (95% CIs). Differences between groups were examined by *t*-test (or Wilcoxon-Mann-Whitney test as appropriate) for continuous variables and by chi-square tests (or Fisher's exact test) of independence for categorical variables.

The IR of serious infections among sustained remission versus sustained LDA groups was examined, and the crude incidence rate ratio (IRR) was calculated with sustained remission as the reference group. The serious infection rates with calculated IRRs were derived from a Poisson level-2 mixed model (i.e., random intercept) with main effect (remission versus LDA status). A Poisson model was chosen because count data were repeatedly drawn from individuals over specified time periods. The Poisson model accounts for the correlation of data within patients and for the clustering of time intervals within patients. Patients could only enter the analysis once since only the first remission episode was used. The model was pre-adjusted for age and sex (i.e., potential variables were retained in the model only if statistical significance achieved a threshold, whereas age and sex were included in all models). Additional analyses examined the IR and IRR of serious infections among patients in the sustained LDA group versus the sustained MHDA group, with the sustained LDA group used as the reference group. In a sensitivity analysis, the IRs and IRRs for serious infections were calculated for the persistent remission group versus the persistent LDA group.

Single factors from the potential confounders were selected as candidate confounders if they altered the estimated IRR for the main exposure outcome associations by more than 10% (17). Covariates were retained as confounders after an assessment of multicollinearity irrespective of whether they were independently associated with the outcome in the fully adjusted model. Adjusted associations were estimated and IRRs were calculated (using the specified reference group) with 95% CIs.

**Ethics.** This study was conducted in accordance with the ethical principles of the Declaration of Helsinki (18). All participating investigators were required to obtain institutional review board (IRB) approval for conducting non-interventional research involving human subjects with a limited data set. Sponsor approval and continuing review were obtained through a central IRB (New England IRB, NEIRB 120160610). For academic investigative sites that did not receive a waiver to use the central IRB, approval was obtained from the respective governing IRBs and documentation of approval was submitted to the sponsor prior to initiating any study procedures. All patients provided consent to participate in the registry. The data used for this study did not include any individually identifiable data. All original data and databases were stored by CORRONA LLC.

## RESULTS

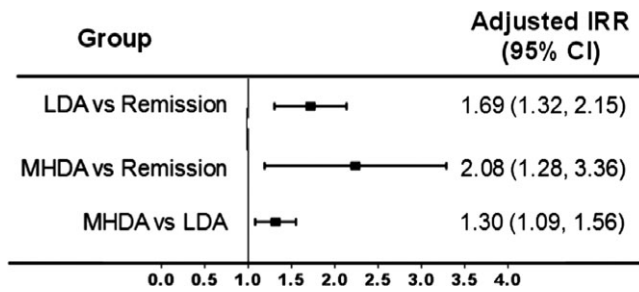
A total of 3,355 patients were included in the sustained remission group, 3,912 in the sustained LDA group, and 5,062 in the sustained MHDA group (Table 1). Most patients in all 3 groups were white females (>70%), with a mean age of approximately 60 years. The mean duration of RA was 9.9 years in the sustained remission group, 12.2 years in the sustained LDA group, and 12.8 years in the sustained MHDA group. Fewer than 18% of patients had a history of nonserious infections in each group. At baseline, prednisone was used at a dose of  $\geq 5$  mg in 4.5% of patients in the sustained remission group, 11.3% of patients in the sustained LDA group, and 15.3% of patients in the sustained MHDA group. The median (IQR) followup time in this analysis was 2.4 (1.1–4.4) years for the sustained remission group, 2.5 (1.2–4.8) years for the sustained LDA group, and 1.7 (0.5–3.7) years for the sustained MHDA group.

Ninety-five patients in the sustained remission group, 214 patients in the sustained LDA group, and 277 patients in the sustained MHDA group developed a serious infection requiring hospitalization or IV antibiotics (Table 2). The crude IR (95% CI) per 100 patient-years for serious infections was 1.03 (0.85–1.26) in the sustained remission group, 1.92 (1.68–2.19) in the sustained LDA group, and 2.51 (2.23–2.82) in the sustained MHDA group (Table 2).

**Table 2. Number of patients with serious infections, patient-years of followup, and crude IRs and unadjusted IRRs for serious infections in patients in sustained remission or sustained disease activity\***

	Sustained remission, n = 3,355	Sustained LDA, n = 3,912	Sustained MHDA, n = 5,062	Remission vs. LDA, P	LDA vs. MHDA, P
Serious infections, no.	95	214	277	–	–
Patient-years of followup	9,182.7	11,169.5	11,049.1	–	–
Crude IR per 100 patient-years (95% CI)	1.03 (0.85–1.26)	1.92 (1.68–2.19)	2.51 (2.23–2.82)	< 0.001	0.003
Adjusted IRR (95% CI) with remission as reference group	1	1.69 (1.32–2.15)	–	–	–
Adjusted IRR (95% CI) with LDA as reference group	–	1	1.30 (1.09 to 1.56)	–	–

\* IRs = incidence rates; IRRs = incidence rate ratios; LDA = low disease activity; MHDA = moderate-to-high disease activity; 95% CI = 95% confidence interval.



**Figure 1.** Adjusted incidence rate ratios (IRRs) for risk of infection. 95% CI = 95% confidence intervals; LDA = low disease activity; MHDA = moderate-to-high-disease activity.

Prednisone dose was the only covariate that met the study criteria as a confounder (data not shown). The adjusted IRR (adjusted for age, sex, and prednisone dose [no dose versus <5 mg versus  $\geq$ 5 mg]) for serious infection was 1.69 (95% CI 1.32–2.15) for sustained LDA versus sustained remission and 1.30 (95% CI 1.09–1.56) for sustained MHDA versus sustained LDA (Figure 1 and Table 2). Prednisone dose of <5 mg was not significant in the sustained LDA versus sustained remission model (IRR 1.31 [95% CI 0.80–2.14]); however, a prednisone dose of  $\geq$ 5 mg conferred a 2-fold increased risk of serious infection (IRR 2.01 [95% CI 1.44–2.82]).

The sensitivity analysis that examined serious infection rates in patients who were persistent in their disease state throughout followup consisted of 1,445 patients in the persistent remission group (43% of patients from the sustained remission group), 1,014 patients in the persistent LDA group (26% of patients from the sustained LDA group), and 1,698 patients in the persistent MHDA group (34% of patients from the sustained MHDA group). The median (IQR) followup time was 2.2 (1.1–3.9) years for the persistent remission group, 1.7 (0.7–3.1) years for the persistent LDA group, and 1.1 (0.2–2.6) years for the persistent MHDA group. When the multivariable model was adjusted for age, sex, and prednisone dose (no dose versus <5 mg versus  $\geq$ 5 mg), the IRR for serious infection in the persistent LDA group versus persistent remission group was 2.08 (95% CI 1.29–3.36), which was similar to the comparison of sustained LDA with sustained remission.

In order to address possible immortal time bias, we further characterized the time between the initial visit and the first followup date for all patients. We observed that all patients identified at the index date also had at least 1 followup visit, reducing concern regarding immortal time bias.

## DISCUSSION

Results from this study of registry data demonstrated that patients in sustained or persistent RA remission had a lower rate of serious infections compared with patients in sustained or persistent LDA. In addition, the incidence of serious infections was reduced in patients in sustained LDA compared with patients in sustained MHDA. Overall, these findings indicate that lower RA disease activity, even between the contrasts of remission and LDA, was associated with a lower risk of serious infections.

In this study, use of glucocorticoid doses at  $\geq$ 5 mg was found to be an independent factor associated with serious infections. A similar finding has been reported in other studies (3,19–23). In the study by Au et al (3), examining disease activity and infection risk in patients with RA from the CORRONA registry, patients receiving a daily prednisone dose of  $\geq$ 7.5 mg had greater than 6 times the rate of infections requiring hospitalization compared with no prednisone use (3). The study by Grijalva et al (22) reported that compared with methotrexate alone, glucocorticoid use at <7.5 mg, 7.5–30 mg, and >30 mg (which follows the definitions for low, medium, and high dose, respectively, described in other reports [24,25]) for treating RA was associated with a dose-dependent increase in the risk of serious infections (22). Several studies have also described how combining TNFi therapy with glucocorticoids to treat RA can increase the risk for infections (19–21,23), with a greater infection risk occurring with higher glucocorticoid doses (>7.5 mg) (20,21).

Common limitations of observational studies apply to the present study. Statistical adjustment for available confounders was performed to balance measured differences between disease activity cohorts, but we cannot exclude the possibility of residual confounding. Since this was an observational study, our observations reflect associations, but causality should not be inferred. In particular, we cannot exclude the possibility that patients with milder disease were more likely to attain and remain in remission. Also, patients were permitted to contribute patient-time to only 1 exposure group, modestly reducing the amount of patient-time available for the analysis. Perhaps more importantly, it may also have resulted in some bias by selecting patients who had stable RA and whose non-RA comorbidities were well controlled. Additionally, a study design that included a time-dependent analysis and allowed patients to contribute patient-time to multiple cohorts, without classifying exposure at the second visit with stable disease and allow infections between the first and second visits, would have affected between-groups differences in infection rates. While our disease activity-based cohorts identified patients at the time they were newly achieving remission or LDA, this study does not directly address the clinical scenario in which a clinician is changing RA treatments for patients starting in low or moderate disease activity in order to attain remission.

A strength of this study is that it analyzed registry data that represent a large number of patients in real-world practice. Patients included in the registry were from a heterogeneous population compared with patients in clinical trials, which usually study patients with severe disease and do not always include patients in remission or LDA. In addition, the patients in this study had newly achieved the disease states of sustained remission and LDA, reflecting a relevant time period for examining if attaining a better disease state provided a health benefit in terms of a lower risk of serious infections. By contributing to the understanding of the potential safety benefits of achieving remission compared to only attaining LDA, this study may assist clinicians and patients in setting RA treatment goals and deciding how aggressively to strive for remission.

## AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Accortt had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study conception and design.** Accortt, Lesperance, Liu, Rebello, Trivedi, Curtis.

**Acquisition of data.** Liu, Rebello, Li, Curtis.

**Analysis and interpretation of data.** Accortt, Lesperance, Liu, Rebello, Trivedi, Li, Curtis.

## ROLE OF THE STUDY SPONSOR

Immunex (Amgen) participated in the analysis and interpretation of the data and in the decision to submit the manuscript for publication. Submission of this manuscript for publication also required the review and approval of all authors. Linda Rice, PhD, at Amgen, provided medical writing assistance and Julia R. Gage, PhD, on behalf of Amgen, provided editorial assistance in the preparation of this manuscript.

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