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Long-Term Safety of Rituximab in Patients With Rheumatoid Arthritis: Results of a Five-Year Observational Study

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Objective. To evaluate the long-term safety of rituximab in an observational cohort of patients with rheumatoid arthritis (RA) who had an inadequate response to ≥1 anti–tumor necrosis factor therapy in the US (SUNSTONE [Study of the Safety of Rituxan in Patients With Rheumatoid Arthritis After an Inadequate Response to Previous Anti-TNF Therapy] registry).

Methods. In this prospective, observational cohort study, patients received rituximab according to their physician's standard practice and were evaluated at standard-of-care follow-up visits at least every 6 months. The primary outcome was the incidence of protocol-defined significant infections. Secondary outcomes included serious adverse events potentially associated with rituximab, cardiovascular or thrombotic events, seizures, deaths, and pregnancies. Post hoc analyses assessed outcomes by concomitant medication use.

Results. Overall, 989 patients (safety-evaluable population) received ≥1 dose of rituximab, with a total follow-up of 3,844 patient-years (mean duration 3.9 years). In total, 341 significant infections occurred in 197 patients (19.9%). The incidence rates (95% confidence intervals [95% CIs]) for significant infections, cardiovascular or thrombotic events, and seizures were 8.87 (95% CI 7.98–9.86), 1.95 (95% CI 1.56–2.45), and 0.18 (95% CI 0.09–0.38) per 100 patient-years, respectively. The incidence of significant infections did not increase with time or with cumulative rituximab exposure. During the study, 64 patients died (crude mortality rate 1.66 per 100 patient-years [95% CI 1.30–2.13]). The most common causes of death were infections (n = 19), malignancy (n = 14), and cardiovascular events (n = 13). Eight pregnancies were reported in 7 patients.

Conclusion. In patients with RA treated with rituximab for up to 5 years, the rates of significant infections were stable over time and higher in patients who received long-term systemic steroid treatment.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease that, if untreated, leads to joint damage and disability. Patients with RA are at a higher risk of infection, lymphomas, and cardiovascular disease (CVD) than the general population (1–4). Biologic disease-modifying antirheumatic drugs (bDMARDs) may elevate the risks of serious infections and malignancies (5–9).

Rituximab is an anti-CD20 monoclonal antibody that targets and depletes CD20-positive B cells and has been shown to be effective for treating RA (10–17). Rituximab, in combination with methotrexate (MTX), is approved to treat RA in patients with an inadequate response to ≥1 anti–tumor necrosis factor (anti-TNF) agent. The safety profile of rituximab for the treatment of RA continues to be defined, and there is a need for high-quality, real-world safety data in addition to the results of randomized clinical trials. In randomized, placebo-controlled trials, the rates of adverse events (AEs) and serious AEs (SAEs) were similar in patients with RA treated with MTX plus rituximab and in those who received MTX plus placebo (10–13,15–18). Open-label fol-

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SIGNIFICANCE & INNOVATIONS

- This 5-year prospective, observational study evaluated the safety of rituximab in combination with methotrexate in patients with rheumatoid arthritis who had a previous inadequate response to ≥1 anti–tumor necrosis factor agent in real-world clinical settings.
- This study sought to characterize the incidence of clinically significant infections, a broadly defined outcome that includes both serious infections and nonhospitalized infections that required treatment with intravenous antibiotics.
- The observed rate of clinically significant infections in this study is between previously reported rates among rituximab-treated patients with rheumatoid arthritis in clinical trials and the US Medicare patient population. Consistent with previous findings, infection rates were stable over time and with repeated rituximab exposure.

low-up of patients (≥11 years) enrolled in randomized clinical trials suggested that incidence rates (IRs) of key AEs remained stable during multiple courses of treatment (≥6), although these data are limited by cohort size and exposure time (19–21). To date, safety data for patients with RA receiving rituximab on a long-term basis in the real-world setting are limited.

SUNSTONE (Study of the Safety of Rituxan in Patients With Rheumatoid Arthritis After an Inadequate Response to Previous Anti-TNF Therapy) was a prospective, observational cohort study designed to evaluate the long-term safety of rituximab in patients with RA in real-world clinical settings in the US, including evaluating the incidence of significant infections and SAEs. The study also provided the opportunity to examine the incidence of malignancies as an exploratory objective.

PATIENTS AND METHODS

Study design and population. The SUNSTONE registry was an observational study designed to follow patients with RA who had an inadequate response to ≥1 anti-TNF agent and who subsequently received rituximab. Patients were recruited to SUNSTONE between January 2007 and October 2008 from 173 private and academic practices across 38 states within the US and Puerto Rico. Inclusion criteria for this study included age ≥18 years, a diagnosis of RA, an inadequate response to ≥1 anti-TNF agent, and no prior use of rituximab, unless received ≤8 weeks before screening. (Investigators of the SUNSTONE registry are shown in Appendix A.)

Patients were treated with rituximab in accordance with their physician's standard practice. Rituximab was administered per the label recommendations for RA (each treatment course consisting of 2 × 1,000-mg intravenous [IV] infusions separated by 2 weeks; courses were repeated every 24 weeks based on clinical evaluation, but not sooner than every 16 weeks) or at the physician's discretion (22). Patients were followed for ≤5 years (end of study) or until death, withdrawal of consent, or loss to follow-up. Follow-up continued regardless of discontinuation of rituximab or switching to another bDMARD. Protocol-specified assessments were completed at screening, at baseline, and at standard-of-care follow-up visits that occurred at least every 6 months and included medical history, current RA disease status, the physician's global assessment, and AEs. Targeted AEs reported during standard-of-care follow-up visits were entered into an electronic case report form. Concomitant medication use was reported by the treating physician. Source documentation for reported events was reviewed during annual site-monitoring visits.

All procedures followed were in accordance with the ethics standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. All investigators obtained institutional review board approval for the investigation, and all patients provided informed consent.

Outcomes. The primary outcome was the incidence of significant infections, defined as any infection that required hospitalization, was life-threatening or fatal, resulted in significant disability, was medically significant in the opinion of the investigator, or required IV antibiotics. Significant infections were confirmed through a review of medical records, diagnostic imaging, and histology or pathology reports, including both cases with and those without culture results. This protocol-defined outcome was selected to provide an inclusive measure of clinically significant infections, including those that were identified as serious infections (SAEs), as well as nonhospitalized infections that required treatment with IV antibiotics. Per protocol, SAEs were defined as any AE that was life-threatening or fatal, required prolonged hospitalization, resulted in significant disability, congenital anomaly, or a birth defect, or was medically significant (in the investigator's opinion). The classification of an infection as opportunistic was based on the investigator's judgment and did not follow any specific guidance. A post hoc case review of opportunistic infections was performed by an expert panel (KLW, KS, and DEF) to adjudicate reported opportunistic infections according to published consensus definitions (23).

Secondary outcomes included the IRs of the targeted AEs, deaths and causes of death, and pregnancies and pregnancy outcomes. Targeted AEs included SAEs suspected to be associated with rituximab or with another treatment as assessed by the investigator, cardiovascular or thrombotic (CVT) events, and seizures. CVT events were defined as myocardial infarction (MI), cerebrovascular accident (CVA), deep vein thrombosis (DVT), and pulmonary embolism (PE). The IRs of malignancies, excluding nonmelanoma skin cancers, were assessed as a post hoc exploratory outcome.

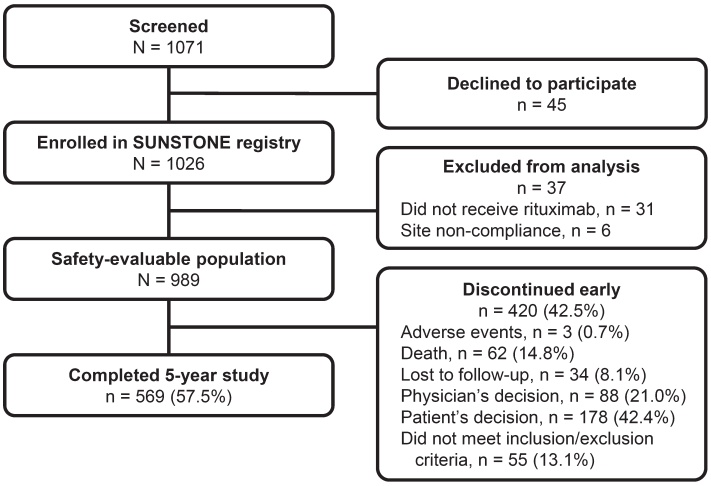


Figure 1. Patient disposition.

Statistical analysis. Descriptive statistics were used to characterize patient demographics, medical history, and treatment patterns during the study period. Estimates of IRs and proportions of patients with safety events were given with 95% confidence intervals (95% CIs). IRs for outcomes expressed as events per 100 patient-years were calculated as the total number of events that occurred during the study period divided by the sum of patient-years of follow-up in the safety-evaluable population, comprising all patients who received rituximab in the study. Patients were followed until the end of the study, death, or loss to follow-up. The 95% CIs of the IRs were calculated based on a normal approximation, under the assumption that the number of events followed a Poisson distribution.

Post hoc subgroup analyses were conducted on 4 treatment subgroups, based on the drug combinations received: neither concomitant conventional synthetic DMARD (csDMARD) nor long-term systemic steroids during the study, long-term systemic steroids but not csDMARD, csDMARD but not long-term systemic steroids, and both csDMARD and long-term systemic steroids. Systemic steroids did not include topical, nasal, or ophthalmic preparations or single-dose intraarticular, single-dose intramuscular, or single-dose IV injections. Long-term systemic steroid use was defined as a patient receiving ≥30 consecutive days of systemic steroids at any point during the study. No multivariate analysis of risk factors was performed.

RESULTS

Patients. Of 1,071 patients screened, 995 were treated with rituximab, and 989 were included in the safety-evaluable population, the primary analysis population for this study (6 patients received rituximab but were excluded due to protocol violations at the study site). A total of 569 patients (57.5%) completed the 5-year study (Figure 1). The safety-evaluable population was 81.8% female and 82.1% white, with a mean ± SD age of 57.3 ± 13.0 years (Table 1). The median RA disease duration was 9 years.

Prior to the study, 936 patients (94.6%) had received ≥1 anti-TNF agent for a median duration of treatment of 3.5 years (interquartile range [IQR] 1.9–5.7), 797 patients (80.6%) had been treated with a csDMARD for a median duration of 6.0 years (IQR 3.0–9.2), and 493 patients (49.8%) had been treated with systemic steroids for a median duration of 4.1 years (IQR 1.8–7.7). At baseline, 767 patients (77.6%) were receiving a concomitant csDMARD and 526 (53.2%) were receiving systemic steroids.

Treatment. A total of 989 patients received ≥1 dose of rituximab during the study, with a total follow-up of 3,844 patient-years. The mean rituximab treatment duration was 3.9 years (median 4.9 years); patients received a mean of 4.0 treatment courses during the entire study follow-up period. Overall, 72% of patients received ≥2 treatment courses of rituximab, 56% ≥3 treatment courses, and 46% ≥4 courses. The median total dose per treatment course was 2,000 mg (range 200–4,000) (1 patient received 2,000 mg twice in the first course of treatment). For all treatment courses, 92% of patients received 2 doses of rituximab during a span of ≤21 days.

At any point during the study period, 890 patients (90.0%) received a concomitant csDMARD. During the study, 786 patients (79.5%) were treated with systemic steroids, 726 patients (73.4%) received long-term systemic steroids (≥30 consecutive days of receiving systemic steroids), and 659 patients (66.6%) received both long-term systemic steroids concomitant with csDMARD treatment during the study. Baseline characteristics were similar across subgroups of patients who did or did not receive a concomitant csDMARD with or without long-term systemic steroid use (see Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23781/abstract). A total of 341 patients (35%) received a different bDMARD following rituximab treatment during the fol-

Table 1. Patient demographics and baseline characteristics*

Characteristic	Safety-evaluable population (n = 989)
Age, mean ± SD years	57.3 ± 13.0
Women	809 (81.8)
Race	
White	812 (82.1)
African American	95 (9.6)
Asian	21 (2.1)
Other	14 (1.4)
Unavailable	47 (4.8)
Ethnicity	
Hispanic/Latino	78 (7.9)
Not Hispanic/Latino	848 (85.7)
Unavailable	63 (6.4)
Disease duration, median (range) years	9.0 (0–62)
RF positivity†	713 (73.9)
PGA, mean ± SD	65.1 ± 21.8
HAQ DI score, mean ± SD	1.48 ± 0.67
Medical history	
Diabetes mellitus	147 (14.9)
Malignancy‡	134 (13.5)
Cardiovascular disease§	579 (58.5)
Infections	325 (32.9)
Opportunistic infections	24 (2.4)
Pulmonary disease	286 (28.9)
Treatment history	
Prior DMARD use, any	976 (98.7)
Prior csDMARD	797 (80.6)
Prior biologic DMARD	945 (95.6)
Prior anti-TNF agent	936 (94.6)
Etanercept	608 (61.5)
Infliximab	597 (60.4)
Adalimumab	500 (50.6)
Systemic steroids	493 (49.8)
Concomitant medications at baseline	
DMARD, any	770 (77.9)
csDMARD	767 (77.6)
Methotrexate	553 (55.9)
Leflunomide	141 (14.3)
Hydroxychloroquine	133 (13.4)
Sulfasalazine	53 (5.4)
Azathioprine	40 (4.0)
Biologic DMARD	9 (0.9)
Anti-TNF agent	8 (0.8)
Systemic steroid	526 (53.2)

* Values are the number (%) unless indicated otherwise. RF = rheumatoid factor; PGA = physician's general assessment; HAQ DI = Health Assessment Questionnaire disability index; DMARD = disease-modifying antirheumatic drug; csDMARD = conventional synthetic DMARD; anti-TNF = anti–tumor necrosis factor.
† n = 965 patients with available data.
‡ The most frequently reported diagnoses were breast cancer (n = 38), basal cell carcinoma (n = 21), melanoma (n = 14), prostate cancer (n = 10), skin cancer (n = 8), colon cancer (n = 8), cervical cancer (n = 6), lymphoma (n = 6), squamous cell carcinoma (n = 6), and non-Hodgkin's lymphoma (n = 5).
§ The most frequently reported diagnoses were hypertension (n = 390) and hyperlipidemia (n = 216). Prior diagnosis of myocardial infarction (n = 46), stroke (n = 35), deep vein thrombosis (n = 33), or pulmonary embolism (n = 16) was infrequent. A history of arterial disease was not specifically collected.

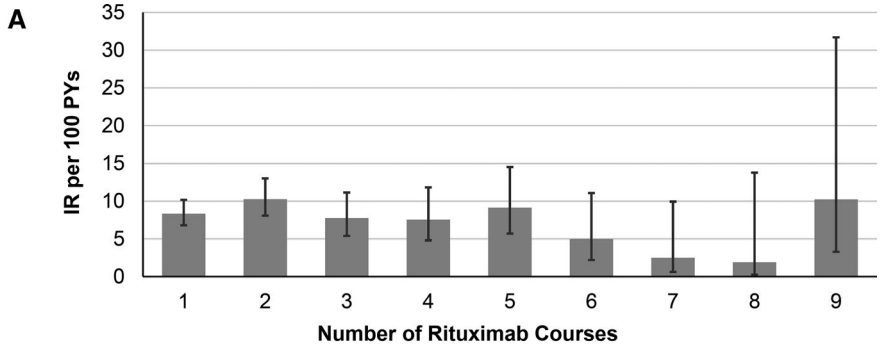
low-up period, with a median washout period of 0.48 years (IQR 0.28–0.76).

Significant infections. A total of 341 significant infections were reported in 197 patients (20%); 78 patients (8%) had ≥2 significant infections. The overall IR of significant infections was 8.87 per 100 patient-years (95% CI 7.98–9.86).

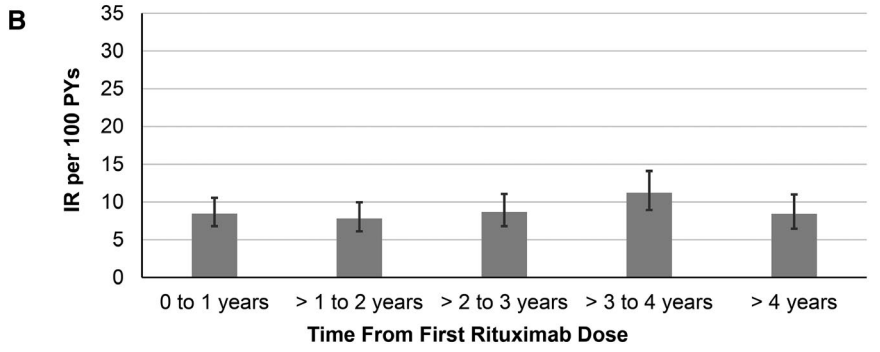
The majority of significant infections (85.6%) were also classified as SAEs, resulting in an IR of serious infections of 7.60 (95% CI 6.77–8.52). The remainder (14.4%) were infections that required IV antibiotics but did not require hospitalization and thus did not meet the definition of an SAE, because the route of treatment was not specified in the definition of an SAE.

The most frequently occurring infections were pneumonia (n = 55 [5.6%]), cellulitis (n = 25 [2.5%]), urinary tract infection (n = 21 [2.1%]), bronchitis (n = 16 [1.6%]), and sepsis (n = 12 [1.2%]). Of the 197 patients who experienced ≥1 significant infection, 77 (39.1%) had an infection in the lower respiratory tract; the most frequently diagnosed type of infection, occurring in 66.0% of patients (130 of 197), was bacterial. No incident cases of tuberculosis were reported.

Opportunistic infections in 15 patients were reported by site investigators. An expert panel adjudicated these cases per consensus definitions and confirmed that 11 patients had opportunistic infections (IR 0.29 per 100 patient-years [95% CI 0.16–0.52]) and 10 had serious opportunistic infections (IR 0.26 per 100 patient-years [95% CI 0.14–0.48]). Of the 11 confirmed opportunistic infections, 8 were fungal (*Aspergillus*, *Candida*, *Histoplasma*, and uncharacterized), and 3 were viral (herpes zoster). The sites of confirmed opportunistic infections included 6 lower respiratory tract, 1 upper respiratory tract, 1 skin, 1 carditis or pericarditis, and 2 other. Four of the 11 confirmed opportunistic infections



Patients, n	905	582	397	300	227	167	123	87	59
Total exposure, PYs	1163.36	662.87	373.95	251.5	185.53	120.31	80.39	51.46	29.31
Number of Events	97	68	29	19	17	6	2	1	3
IR per 100 PYs	8.34	10.26	7.76	7.55	9.16	4.99	2.49	1.94	10.23
(95% CI)	(6.83, 10.17)	(8.09, 13.01)	(5.39, 11.16)	(4.82, 11.84)	(5.70, 14.74)	(2.24, 11.10)	(0.62, 9.95)	(0.27, 13.80)	(3.30, 31.73)



Patients, n	988	895	793	701	630
Total exposure, PYs	943.52	844.23	747.43	667.12	639.17
Number of Events	80	66	65	75	54
IR per 100 PYs	8.48	7.82	8.70	11.24	8.45
(95% CI)	(6.81, 10.56)	(6.14, 9.95)	(6.81, 11.09)	(8.97, 14.10)	(6.47, 11.03)

Figure 2. Incidence rates of significant infection by number of rituximab courses (**A**), and over time (**B**). IR = incidence rate; PYs = patient-years; 95% CI = 95% confidence interval.

occurred ≥6 months after the last rituximab infusion. One of the confirmed cases (reported as a fungal infection of eosinophilic pneumonia) did not fully meet the consensus definition nor could it be excluded based on available laboratory data; this case was judged by the expert panel as a confirmed opportunistic infection and included in the calculated IR.

The rate of significant infections did not increase with the number of successive rituximab courses or with time from rituximab initiation (Figure 2). Rates of significant infections increased with patient age, body mass index (BMI), and baseline Health Assessment Questionnaire disability index (HAQ DI) score; rates of significant infections were also elevated in patients with diabetes or with a prior infectious event <1 year prior to baseline (Figure 3 and Supplementary Table 2, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23781/abstract).

Significant infections occurred at similar rates in patients who had received prior treatment with systemic steroids and those who had not (IR 9.03 [95% CI 7.79–10.48] versus 8.71 [95% CI 7.48–10.13]), but rates were higher in patients who received concomitant long-term systemic steroids than in those who did not (IR 9.71 [95% CI 8.63–10.92] versus 6.43 [95% CI 5.02–8.23]) (Figure 3 and Supplementary Table 2, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23781/abstract). The IR of significant infection events was similar in patients who received concomitant csDMARDs and those who did not (IR 8.86 [95% CI 7.93–9.90] versus 9.02 [95% CI 6.23–13.06]). These trends held across treatment subgroups of patients with or without long-term systemic steroid use during the study and those who did or did not receive a concomitant csDMARD (see Supplementary Table 3, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.23781/abstract). Among the 340 patients who switched to another bDMARD following rituximab treatment, the rate of significant infections was not significantly higher after the switch compared with before the switch (IR 8.23 [95% CI 6.59–10.29] versus 7.04 [95% CI 5.20–9.52]).

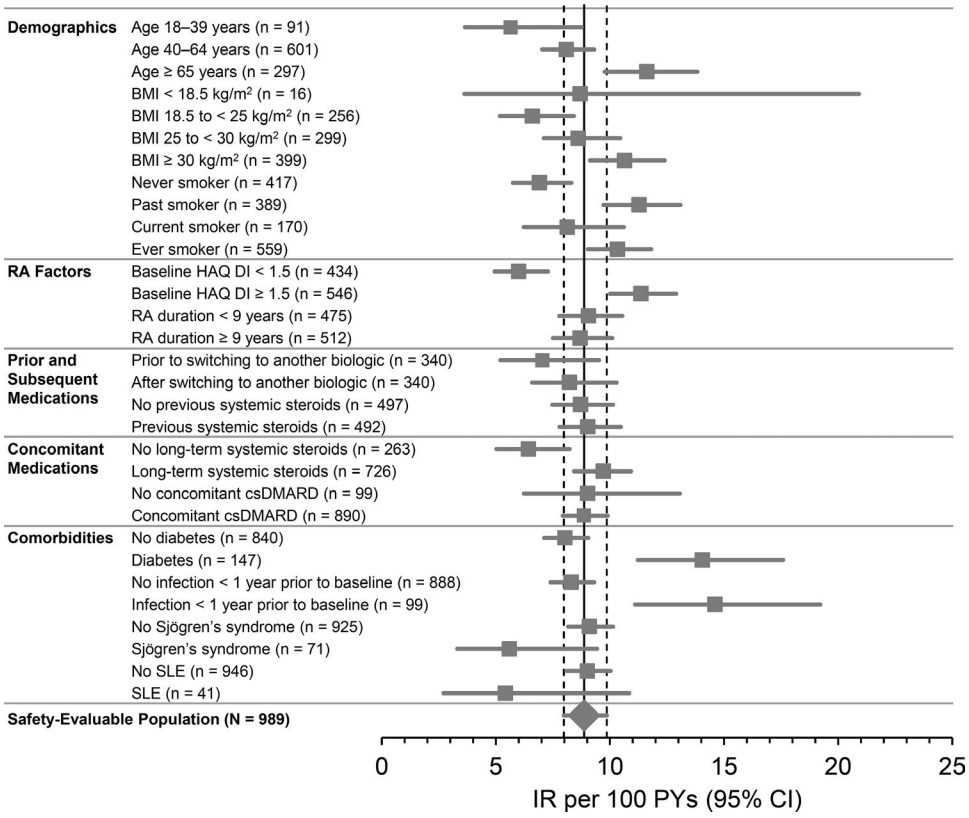


Figure 3. Incidence rates of significant infection by demographics, disease characteristics, rheumatoid arthritis (RA) treatment, medications, and comorbidities. The large diamond and solid vertical line show the incidence rate of significant infections for the entire safety-evaluable population (dashed lines show 95% confidence intervals [95% CIs]). BMI = body mass index; HAQ DI = Health Assessment Questionnaire disability index; csDMARD = conventional synthetic disease-modifying antirheumatic drug; SLE = systemic lupus erythematosus; IR = incidence rate; PYs = patient-years.

SAEs. A total of 544 SAEs were observed in 294 patients (29.7%) during the study; 53.7% of all SAEs (292 of 544) were infections that were also included within the primary outcome of significant infections. The most frequent SAE categories were infections and infestations (n = 163 [16.5%]), cardiac disorders (n = 46 [4.7%]), and respiratory, thoracic, and mediastinal disorders (n = 44 [4.4%]). The most frequently occurring SAEs were pneumonia (n = 53 [5.4%]), urinary tract infection (n = 19 [1.9%]), MI (n = 18 [1.8%]), CVA (n = 17 [1.7%]), cellulitis (n = 16 [1.6%]), bronchitis (n = 14 [1.4%]), DVT (n = 12 [1.2%]), sepsis (n = 11 [1.1%]), and PE (n = 10 [1.0%]). Fourteen patients (1.4%) experienced an SAE that led to discontinuation of rituximab treatment or study termination.

CVT events. A history of cardiovascular disease was reported in 579 patients (58.5%), primarily hypertension (39.4%) and hyperlipidemia (21.8%), with a low prevalence (<5%) for prior MI and CVA (Table 1). A total of 75 CVT events were reported in 65 patients (6.6%). The majority of CVT events (85.3%) were classified as SAEs. Of the CVT events reported, 22 were CVA (n = 21 patients [2.1%]), 22 were MI (n = 20 patients [2.0%]), 16 were DVT (n = 16 patients [1.6%]), 10 were PE (n = 10 patients [1.0%]), and 5 were classified as other types of CVT events.

The IRs of overall and serious CVT events were 1.95 (95% CI 1.56–2.45) and 1.66 (1.30–2.13) per 100 patient-years, respectively. The overall IRs of MI, CVA, DVT, and PE were 0.57 (95% CI 0.38–0.87), 0.57 (95% CI 0.38–0.87), 0.42 (95% CI 0.25–0.68), and 0.26 (95% CI 0.14–0.48) per 100 patient-years, respectively (Figure 4).

In patients who switched to another bDMARD following rituximab treatment, the rate of CVT events did not increase after initiation of the new bDMARD compared with the period prior to initiation (rate ratio 1.13 [95% CI 0.47–2.90]) (see Supplementary Table 4, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23781/abstract). The IRs of MI, CVA, DVT, and PE prior to versus after switching to another bDMARD were 0.67 (95% CI 0.25–1.78) versus 0.43 (95% CI 0.16–1.14), 0.17 (95% CI 0.02–1.19) versus 0.53 (95% CI 0.22–1.28), 0.33 (95% CI 0.08–1.34) versus 0.32 (95% CI 0.10–0.99), and 0.33 (95% CI 0.08–1.34) versus 0.32 (95% CI 0.10–0.99), respectively.

IRs of CVT events increased with age, BMI, baseline HAQ DI score, RA duration, the number of prior DMARDs, and a history

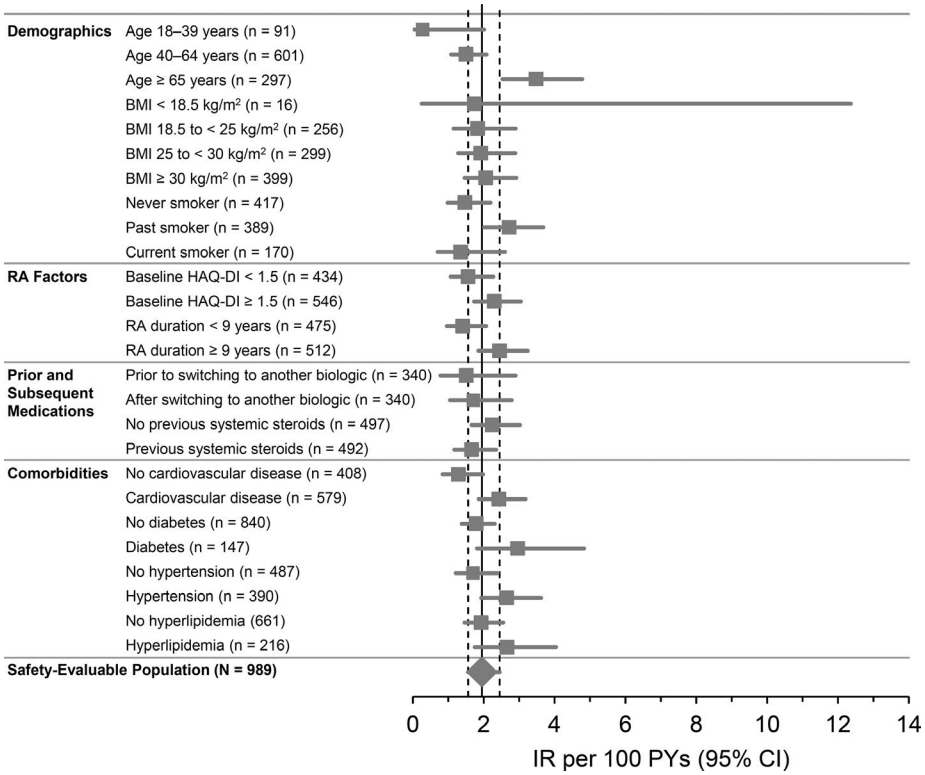


Figure 4. Incidence rates of cardiovascular or thrombotic (CVT) events by demographics, disease characteristics, rheumatoid arthritis (RA) treatment, medications, and comorbidities. The large diamond and solid vertical line show the incidence rate of CVT events for the entire safety-evaluable population (dashed lines show 95% confidence intervals [95% CIs]). BMI = body mass index; HAQ DI = Health Assessment Questionnaire disability index; IR = incidence rate; PYs = patient-years.

of cardiovascular disease, diabetes, hypertension, hyperlipidemia, and smoking (Figure 4 and Supplementary Table 4, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23781/abstract). The IRs of CVA, MI, PE, and DVT were similar across treatment subgroups of patients with or without long-term systemic steroid use during the study and those who did or did not receive a concomitant csDMARD (see Supplementary Table 3, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.23781/abstract).

Seizures or altered mental status. Six patients (0.6%) experienced 7 seizure events or episodes of serious altered mental status. Of these, 2 were considered serious (1 convulsion, 1 delirium). None of these events occurred during rituximab administration. Of the 6 patients who experienced seizure, 5 had a history of seizure.

The IR of seizure or altered mental status was 0.18 per 100 patient-years (95% CI 0.09–0.38). There were no significant differences in this rate between treatment subgroups, although no seizures occurred in patients who did not receive systemic steroids long term (see Supplementary Table 3, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23781/abstract).

Deaths and loss to follow-up. There were 64 deaths (6.5%) during the 5-year follow-up. The most common causes of death were infection (n = 19 [1.9%]), malignancies (n = 14 [1.4%]), and CVD (n = 13 [1.3%]). Of the fatal infections, 7 were characterized as sepsis, 5 as pneumonia, 2 as both pneumonia and sepsis (1 patient also had congestive heart failure and CVA), and 1 each as peritonitis (resulting in cardiac arrest), aspergillosis, diverticulitis, fungal endocarditis, and hepatitis C. The time between a patient's last rituximab infusion and death caused by an infection varied widely (median 262 days [range 38–1,687]) (see Supplementary Figure 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23781/abstract).

The crude mortality rate was 1.66 per 100 patient-years (95% CI 1.30–2.13). After standardization to 2010 age- and sex-specific all-cause mortality rates from the US general population, the standardized mortality rate was 1.58 per 100 patient-years (95% CI 1.22–2.01).

During the study period, 22 patients were lost to follow-up. Upon inquiry by the researchers, 12 patients were confirmed by the clinical site to be alive, and 2 were reported to have died and were included in the total number of deaths above.

Pregnancies. Of the 809 female patients, 7 reported a total of 8 pregnancies during the study. Two pregnancies ended

in spontaneous abortion (2 months) and 1 ended in elective termination (10 weeks). The remaining 5 pregnancies resulted in live births, with 1 premature birth. No congenital anomalies were reported.

Malignancies. A history of malignancy was reported in 134 patients (13.5%) (Table 1). There were 17 incident malignancies (by the treating clinician's assessment) in 17 patients (1.7%). Lung cancer was the most common malignancy reported (n = 5 patients [0.5%]), followed by breast cancer (n = 2 patients [0.2%]) and melanoma (n = 2 patients [0.2%]). Incident colon cancer, acute myeloid leukemia, pancreatic carcinoma, bladder cancer, adenocarcinoma, and adenoid cystic carcinoma were each reported in 1 patient. A new or secondary malignancy was diagnosed in 7 patients with a history of malignancy, including 2 cases of recurrent melanoma and 1 of recurrent lung cancer. Metastatic neoplasm was reported in 2 patients without a specific site reported. The overall crude and the age- and sex-standardized IRs of malignancies were 0.44 (95% CI 0.27–0.71) and 0.36 per 100 patient-years (95% CI 0.21–0.57), respectively.

Malignancy diagnoses occurred a median of 22 months after rituximab initiation (range 2.6–59 months) and following a median of 2 treatment cycles. A history of malignancy, advanced age, and current or prior tobacco use were more common among patients in whom incident malignancy was diagnosed.

DISCUSSION

This study shows long-term safety data for 989 patients with RA who were treated with rituximab. The study provides extensive characterizations of clinically relevant infections, CVT events, malignancies, and other serious events in patients with RA treated with rituximab in real-world clinical practice settings.

SUNSTONE shows an overall IR of significant infections in the safety-evaluable population of 8.87 per 100 patient-years and an IR of more narrowly defined serious infections (infections categorized as SAEs) of 7.60 per 100 patient-years. These observed IRs fall between previously reported IRs of serious infections in patients with RA treated with rituximab. The IR of serious infections in SUNSTONE exceeded those reported in the global, pooled clinical trial population of patients treated with rituximab (n = 3,595) with up to 11 years of follow-up (IR 3.76 per 100 patient-years), in patients with RA enrolled in the US-based Corrona registry (IR 1.6 per 100 patient-years), and in patients with RA treated with csDMARDs and anti-TNF agents in the UK-based British Society for Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR-RA) (IR 3.2 and 4.2 per 100 patient-years, respectively) (21,24,25). There was a greater IR incidence of opportunistic infections in patients in SUNSTONE compared with rituximab-treated patients in the BSRBR-RA (0.29 versus 0.15 per 100 patient-years) (26). However, the IR of serious infections in SUNSTONE was lower than the IR of hospitalized infections (identified in inpatient hospital discharge diagnosis data) in rituximab-treated patients in the US Medicare population (18.7 per 100 patient-years) (27).

Differences in patient populations may explain the differences in observed rates of significant or serious infections. Unlike the overall rituximab clinical trials population, SUNSTONE required an inadequate response to ≥1 anti-TNF agent, a factor associated with an increased risk of infection in RA, and patients in SUNSTONE who switched to another bDMARD continued to be followed (28,29). When comparing patients enrolled in Corrona with those in SUNSTONE, we found that patients in SUNSTONE had higher disease activity (mean HAQ DI score 1.48 versus 0.65) and more frequent glucocorticoid use (53.2% versus 35.5%), which may increase the risk of infection (24). Additionally, IRs reported from long-term follow-up of the randomized trial population may reflect enrichment for the patients who do not withdraw from long-term extension studies due to loss of response or the development of AEs. Importantly, the rate of significant infections did not increase over time or with the number of courses of rituximab, reflecting similar findings for the rate of serious infections in both clinical trial populations and in patients treated with rituximab in real-world settings (20,21,24,30).

The overall IR of CVT events in this study was consistent with the previously reported rate of cardiovascular events in patients with RA treated with rituximab in real-world settings (1.95 versus 1.6 per 100 patient-years) (24). The rates of CVA and MI in this study were consistent with those previously reported in the pooled clinical trial populations of patients treated with rituximab and concomitant MTX (0.57 and 0.57 versus 0.19 and 0.41 per 100 patient-years, respectively) (20). DVT and PE in SUNSTONE occurred at rates consistent with those reported in a claims-based study of patients with RA (0.42 and 0.26 versus 0.21 and 0.15 per 100 patient-years, respectively) (31). The standardized IR of malignancies (0.36 per 100 patient-years) was not elevated compared with the expected rate of malignancies in the background population (1.0 per 100 patient-years) or compared with IRs observed in rituximab clinical trial populations (0.69–0.74 per 100 patient-years) (20,21,32).

Patients with RA are at a moderately elevated risk of malignancy compared with the general population (33). However, the overall IR of malignancy was low in the SUNSTONE population compared with previous registry studies (24, 34). Notably, both anti–TNF- and rituximab-treated patients in the BSRBR-RA had a lower incidence of malignancy than patients treated with csDMARDs alone (34). Taken together, these data support the recommendation for rituximab to treat RA in patients who have a history of malignancy.

This study has some important limitations. Rituximab dosage, frequency, and duration were not mandated by the study protocol, and some variability was observed between patients. Additionally, the dosages and types of concomitant medications

were managed without restriction by the treating physician. The study did not collect longitudinal data on disease activity or treatment response, because open-label data are subject to significant selection and observational biases. Both the number and types of prior treatments varied widely between patients. Several details of interest regarding infection events were not captured per the protocol; these included vaccination history, immunoglobulin levels, bacterial cultures, and IV steroid use with rituximab infusion. Finally, with limited follow-up and no data linkage to national data sources to assure full capture of all safety events, some anticipated events may have been underreported. The results reported here must be interpreted in light of the real-world nature of the SUNSTONE registry and these sources of variability.

This 5-year observational study evaluated the safety of rituximab in combination with MTX for the treatment of RA among patients with an inadequate response to ≥1 anti-TNF agent in a real-world clinical practice setting. For most key AEs, IRs were similar to those in the historical data. However, the rates of clinically significant infections in this cohort of patients refractory to treatment with prior exposure to biologic therapies were higher than those observed in other clinical trial or registry populations of rituximab-treated patients with RA, but lower than those reported in a similar cohort of the Medicare population. Rates were elevated in patients receiving long-term concomitant glucocorticoids. Consistent with previous findings, infection rates were stable over time and with repeated rituximab exposure. No new safety signals were observed.

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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. Winthrop 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.

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