Nonserious Infections in Patients With Rheumatoid Arthritis: Results From the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis

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Objective. To describe the frequency and predictors of nonserious infections (NSI) and compare incidence across biologic agents within the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR-RA).

Methods. The BSRBR-RA is a prospective observational cohort study. An NSI was defined as an infection that did not require hospitalization or intravenous therapy. Infections were captured from clinician questionnaires and patient diaries. Individuals were considered “at risk” from the date of initiation of biologic treatment for up to 3 years. Drug exposure was defined by agent: tumor necrosis factor inhibitor (TNFi), interleukin-6 (IL-6) inhibitor, B cell depletion (rituximab), or conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) alone. A multiple-failure Cox model was used with multivariable adjustment. Missing data were addressed using multiple imputation.

Results. There were 17,304 NSI in 8,145 patients, with an event rate of 27.0 per person per year (95% confidence interval [95% CI] 26.6–27.4). Increasing age, female sex, comorbidity burden, glucocorticoid therapy, higher Disease Activity Score in 28 joints, and higher Health Assessment Questionnaire disability index were associated with an increased risk of NSI. There was a significant reduction in NSI risk with csDMARDs compared to biologic treatments. Compared to TNFi, IL-6 inhibition and rituximab were associated with a higher NSI risk (adjusted hazard ratio 1.45 [95% CI 1.29–1.63] and adjusted hazard ratio 1.28 [95% CI 1.14–1.45], respectively), while the csDMARD cohort had a lower risk (adjusted hazard ratio 0.64 [95% CI 0.59–0.70]). Within the TNFi class, adalimumab was associated with a higher NSI risk than etanercept (adjusted hazard ratio 1.11 [95% CI 1.05–1.17]).

Conclusion. NSI occur frequently in RA, and predictors mirror those reported with serious infections. All biologics are associated with a greater risk of NSI, with differences observed between agents. While unmeasured confounding must be considered, the magnitude of effect is large, and a relationship between NSI and targeted immunomodulatory therapy likely exists.
INTRODUCTION

Patients with rheumatoid arthritis (RA) experience a greater number of infections compared to the background population. These infections are frequent and contribute to substantial morbidity and mortality (1,2). Infection susceptibility is a combination of disease-related immunologic dysfunction, immunocompromising comorbidities, and the use of immunomodulatory drugs. It is also determined by patient lifestyle and other factors beyond the RA disease.

The risk of serious infections, defined as life-threatening infections or those requiring hospitalization or intravenous antibiotics, has been an important focus of long-term clinical trial extension studies and observational drug registries. Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) have relatively little impact (3,4), glucocorticoids consistently demonstrate a dose-dependent risk (5,6), and biologics are associated with a small but significant risk of serious infection (7–10). Differences in risk observed between biologic agents have particular clinical relevance for patients considered to be “high risk” (8,10,11).

Serious infections are the tip of the iceberg. Nonserious infections (NSI), defined as those events managed outside of a hospital admission, have been reported in 20–30% of RA patients each year (1,12) and are the most common adverse events in large clinical trials. In elderly RA patients, rates of NSI are estimated at 47.5 per 100 patient-years (13). Although these events are not life-threatening, their burden is high (14), and recurrent NSI may lead to variable periods of treatment discontinuation (15). Meta-analyses of data on immune-mediated inflammatory diseases have suggested differences in the risk of NSI between tumor necrosis factor inhibitor (TNFi) agents (14), but the impact of other biologics and the predictors of such risk are less well understood.

Despite extensive literature on infection in RA, data on NSI are limited. To our knowledge, there has been little research on variables that predict NSI in patients with RA and the extent to which immunomodulatory drugs influence this risk. The primary objective of this study was to describe the frequency and pattern of NSI and to compare the incidence of NSI between biologic drugs within a large national registry.

PATIENTS AND METHODS

Patient population. Study subjects were participants in the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR-RA) (Appendix A), a national prospective observational cohort study established in 2001 to monitor long-term safety of biologic therapy. Initial biologic cohorts were for patients receiving etanercept and infliximab. The csDMARD cohort was recruited in parallel between 2002 and 2009. Subjects had moderate-to-severe disease activity but were not eligible for biologic treatment. Adalimumab, rituximab, tocilizumab, and certolizumab pegol cohorts were recruited beginning in 2004, 2008, and 2010, respectively, while JAK inhibitor (tofacitinib and baricitinib) and sarilumab cohorts were recruited beginning in 2017/2018. Abatacept and golimumab cohorts were not recruited. The BSRBR-RA methodology has been previously described in detail (16). Ethics approval was granted in 2000 (MREC no. 00/8/053 [IRAS no. 64202]). The data cutoff date for this study was January 2019.

Baseline assessment. Data collected at registration included demographic information, disease duration, smoking status, DMARD and glucocorticoid exposure, Disease Activity Score in 28 joints using the erythrocyte sedimentation rate (DAS28-ESR) (17), Health Assessment Questionnaire (HAQ) (18) scores, and comorbidities (yes/no) from a list. For analysis, comorbidity burden was scored using the Rheumatic Disease Comorbidity Index (19).

Follow-up. Follow-up data were collected every 6 months for the first 3 years via questionnaires sent to patients and their supervising rheumatology teams, and annually thereafter via questionnaires sent only to the supervising rheumatology team. Data on adverse events were captured from clinician questionnaires: from patient diaries every 6 months and by linkage to NHS Digital, which provides mortality data. Patient diaries were provided for the first 3 years, in which patients were asked to record details of all new prescriptions (including antibiotics) and hospital attendances. Patient-reported serious adverse events required verification by the supervising rheumatology team. No additional verification of nonserious adverse events occurred, but all reported NSI were recorded in the database and coded.

Outcome measure. The primary outcome measure was an NSI reported to the BSRBR-RA by either the clinical team or the patient. Infections were coded using terminology from the Medical Dictionary for Regulatory Activities (MedDRA), and their severity was recorded according to the established MedDRA definition as an infectious episode that did not require hospitalization or intravenous therapy or lead to severe disability or death.

Exposure. Individuals were considered “at risk” from the date of beginning their first registered biologic treatment for up to 3 years, or until the date of treatment discontinuation, last received follow-up, or death, whichever came first. Censorship at 3 years was aligned to the time frame when diaries were collected, which was a key source of NSI. Patients could discontinue or switch therapies during the 3-year period, and all biologic exposure during this 3-year window was included. A switch to another biologic during this time would not extend the total follow-up window past 3 years, as diary collection terminated 3 years after registration. For example, if a patient started a subsequent biologic treatment after 2 years, they would only contribute a maximum of 1 year of exposure to this second biologic.
Due to the BSRBR-RA study design, hospitals had the option of re-registering existing study patients with the BSRBR-RA at the point of a patient switching to a therapy for which a cohort was actively being recruited. For example, a patient recruited in 2003 at the point of starting etanercept could then re-register in 2012 with a new study ID number when starting a new biologic treatment. All subsequent follow-up time would be transferred to the new study ID, but the 2 IDs would be linkable in the data set. This increased the frequency of follow-up and restarted diary capture for a further 3 years.

To account for ongoing exposure risk from the biologic’s half-life after stopping therapy, an additional 90 days of exposure time was considered for all biologics. For rituximab, an additional 180 days of exposure time was considered, although in all cases it was censored at the maximum 3-year cutoff.

**Statistical analysis.** Crude incidence rates per 100 patient-years with 95% confidence intervals (95% CIs) were calculated. A multiple-failure Cox proportional hazards model was used to compare risk of NSI across groups, since many patients

| Table 1. Baseline characteristics of the BSRBR-RA population* |
|---------------------------------------------------------------|
| **BSRBR-RA population** | **Biologic treatment at registration** |
| | No biologic | TNFi | IL-6 | Rituximab |
| | (n = 23,584)† | (n = 3,480) | (n = 17,488) | (n = 1,025) | (n = 1,255) |
| Age, mean ± SD years | 56.6 ± 12.9 | 60.0 ± 12.5 | 55.6 ± 13.0 | 57.6 ± 12.1 | 59.4 ± 12.1 |
| Female sex | 17,319 (73.4) | 2,533 (72.8) | 12,777 (73.1) | 799 (78.0) | 959 (76.4) |
| Smoking status | | | | | |
| Current smoker | 4,701 (21.2) | 810 (23.5) | 3,527 (21.0) | 133 (17.7) | 182 (21.6) |
| Ex-smoker | 8,438 (37.8) | 1,392 (40.4) | 6,305 (37.5) | 279 (37.2) | 347 (41.3) |
| Cardiovascular disease§ | 1,975 (8.4) | 427 (12.3) | 1,252 (7.2) | 101 (9.9) | 169 (13.5) |
| Respiratory disease§ | 3,799 (16.1) | 661 (19.0) | 2,609 (14.9) | 207 (20.2) | 272 (21.7) |
| Disease duration, median (IQR) years | 10 (4–18) | 6 (1–15) | 10 (5–18) | 10 (5–19) | 12 (6–20) |
| Steroid use as baseline | 8,151 (34.6) | 804 (23.1) | 6,398 (36.6) | 311 (30.3) | 511 (40.7) |
| Concurrent DMARD use | | | | | |
| No DMARDs | 4,806 (20.4) | 29 (0.8) | 4,131 (23.6) | 275 (26.8) | 234 (18.7) |
| MTX only | 8,813 (37.4) | 1,224 (35.2) | 6,487 (37.1) | 397 (38.7) | 610 (48.6) |
| Sulfasalazine only | 1,080 (4.6) | 448 (12.9) | 551 (3.2) | 31 (3.0) | 37 (3.0) |
| Leflunomide only | 1,144 (4.9) | 265 (7.6) | 761 (4.4) | 39 (3.8) | 64 (5.1) |
| HCQ only | 547 (2.3) | 79 (2.3) | 379 (2.2) | 44 (4.3) | 32 (2.6) |
| Other DMARD only | 657 (2.8) | 162 (4.7) | 444 (2.5) | 11 (1.1) | 36 (2.9) |
| 2 DMARDs | 5,115 (21.7) | 996 (28.6) | 3,700 (21.2) | 186 (18.2) | 185 (14.7) |
| ≥3 DMARDs | 1,416 (6.0) | 275 (7.9) | 1,031 (5.9) | 42 (4.1) | 57 (4.5) |
| No. of previous DMARDs, median (IQR) | 3 (2–4) | 2 (1–3) | 3 (2–4) | 3 (2–3) | 3 (2–4) |
| Baseline DAS28-ESR, median (IQR) | 6.10 (5.29–6.91) | 5.15 (4.32–6.03) | 5.39 (5.1–7.05) | 5.05 (5.65–5.50) | 5.15 (5.33–5.88) |
| TJC | 13 (7–20) | 7 (3–12) | 14 (8–21) | 12 (7–19) | 13 (8–20) |
| SJC | 8 (4–13) | 5 (2–8) | 9 (5–14) | 6 (4–10) | 8 (4–12) |
| PtGA | 73 (54–84) | 55 (40–75) | 75 (60–85) | 75 (60–84) | 73 (56–83) |
| ESR | 34 (18–57) | 29 (16–48) | 36 (19–59) | 25 (10–46) | 36 (20–62) |
| Baseline CRP, median (IQR) | 20 (7–46) | 18 (7–42) | 21 (8–49) | 12 (5–35) | 21 (8–45) |
| Baseline HAQ DI score, median (IQR) | 2 (1.38–2.38) | 2 (1.23) | 2 (1.5–2.38) | 2 (1.38–2.25) | 2 (1.63–2.38) |
| First exposure to biologic drug | 19,538 (82.8) | – | 15,200 (86.9) | 232 (22.6) | 262 (20.9) |
| Proportion of patients remaining in baseline drug cohort for 3-year window¶ | 16,074 (68.1) | 2,899 (83.3) | 12,115 (69.3) | 630 (61.5) | 430 (34.3) |
| Calendar year of start, median (IQR) | 2005 (2004–2011) | 2005 (2004–2006) | 2005 (2003–2012) | 2014 (2012–2016) | 2010 (2009–2011) |

* Except where indicated otherwise, values are the number (%) of patients. Due to study design, hospitals had the option of re-registering existing study patients with the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR-RA) at the point of them switching to a therapy cohort that was actively recruiting patients. This occurred with 1,174 patients, 5% of the total cohort. Where this occurs, patients are included each time in the table. TNFi = tumor necrosis factor inhibitor; IL-6 = interleukin-6; RDCI = Rheumatic Disease Comorbidity Index; IQR = interquartile range; DMARD = disease-modifying antirheumatic drug; MTX = methotrexate; HCQ = hydroxychloroquine; DAS28-ESR = Disease Activity Score in 28 joints using the erythrocyte sedimentation rate; TJC = tender joint count; SJC = swollen joint count; PtGA = patient global assessment; CRP = C-reactive protein; HAQ DI = Health Assessment Questionnaire disability index.
† The Cox proportional hazards model allowed patients to stop or switch therapies during the 3-year period. The data presented in this table refer to the patients in each drug cohort at BSRBR-RA registration and do not reflect the characteristics of patients who may have switched into a new drug cohort during the analysis window.
‡ The total BSRBR-RA population includes patients commencing receiving JAK inhibitor therapy and anakinra. As these drug classes were excluded from the analysis, their individual baseline data are not presented here.
§ Included ischemic heart disease and cerebrovascular accidents.
¶ The BSRBR-RA study design, hospitals had the option of re-registering existing study patients with the BSRBR-RA at the point of a patient switching to a therapy for which a cohort was actively being recruited. For example, a patient recruited in 2003 at the point of starting etanercept could then re-register in 2012 with a new study ID number when starting a new biologic treatment. All subsequent follow-up time would be transferred to the new study ID, but the 2 IDs would be linkable in the data set. This increased the frequency of follow-up and restarted diary capture for a further 3 years.
NONSEROUS INFECTION RISK IN RA

The TNFi class was chosen as the referent for comparison, as the number of patients receiving these medications was low or absent.

Potential confounders were selected a priori based on clinical knowledge and available variables. Adjustments included age, sex, disease duration, smoking, baseline DAS28-ESR, HAQ disability index (HAQ DI), steroid treatment, and year recruited to the BSRBR-RA. When a patient switched drugs, baseline characteristics were updated and reflected in the multivariate model. The number of biologic agents prescribed since registration was included as a time-varying covariate to adjust for the effect of switching treatments. A patient who switched biologics due to an infection had an increased risk of recurrent infection with their next drug (20). To account for competing risks and to adjust for clustering of events within individuals, the number of cumulative serious infections and NSI were also included as time-varying covariates. Assumptions of the Cox model were tested using Nelson-Aalen plots. Missing data were addressed using multiple imputation with chained equations for 20 cycles (Supplementary Methods and Supplementary Tables 1 and 2, available on the Arthritis & Rheumatology website at http://onlinelibrary.wiley.com/doi/10.1002/art.41754/abstract). Results between the unimputed and imputed models were compared. Analyses were undertaken using Stata 15.

Sensitivity analysis. Analyses using different drug exposure windows, limited to “on-drug time only” (excluding the 3- or 6-month half-life exposure risk) and also extended to an “ever-exposed” model until point of switch, were compared. Risk of NSI by method of ascertainment was also examined. To account for patients who registered a second time within the BSRBR-RA and contributed to more than 1 drug cohort, we recalculated SEs and contributed to more than 1 drug cohort, we recalculated SEs using the cluster-robust sandwich estimator, accounting for the within-individual correlation across these different observations. To account for the effect of serious infection, sensitivity analyses using a single-failure model were performed incorporating serious infection as a competing risk using the Fine and Gray method (21).

RESULTS

Patient characteristics. A total of 23,584 patients were registered in the BSRBR-RA until January 2019. The baseline characteristics are listed in Table 1. The mean age was 57 years, and the median disease duration was 10 years. The median base-

| Table 2. Number and type of NSI reported during the 3-year follow-up period* |
|----------------------------------|------------------|------------------|------------------|------------------|
| Person-years                     | 64,034           |
| Total no. of recorded NSI       | 17,602           |
| Patients with infection         | 8,145            |
| No. of infections per patient, median (IQR) (max = 22) | 1 (1–3) |

| Organ involvement | Respiratory | Urinary | ENT | Skin | Oral | Musculoskeletal | GI | Ocular | Genital | Neurologic | Other |
|-------------------|-------------|---------|-----|------|------|----------------|----|--------|---------|------------|-------|
|                   | 6,268       | 2,921   | 2,486 | 1,850| 791  | 744            | 277| 482    | 143     | 2          | 1,638 |

* More than 1 infection could be listed for the same date. NSI = nonserious infections; IQR = interquartile range; ENT = ear, nose, and throat; GI = gastrointestinal; NTM = nontuberculous mycobacteria; HBV = hepatitis B virus; PML = progressive multifocal leukoencephalopathy; PCP = Pneumocystis jirovecii pneumonia.

experienced multiple events. A traditional (single-failure) model examining time to first event would ignore any additional infections, overlooking important information to enable us to understand risk. We therefore used a multiple-failure model, allowing patients to contribute more than 1 event and in which dependency in the hazard function was modeled as a shared frailty (i.e., random effect). Cluster-robust estimates for CIs were calculated. The risk of NSI were also included as time-varying covariates. Assumptions of the Cox model were tested using Nelson-Aalen plots. Missing data were addressed using multiple imputation with chained equations for 20 cycles (Supplementary Methods and Supplementary Tables 1 and 2, available on the Arthritis & Rheumatology website at http://onlinelibrary.wiley.com/doi/10.1002/art.41754/abstract). Results between the unimputed and imputed models were compared. Analyses were undertaken using Stata 15.

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RESULTS

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line DAS28-ESR was 6.10 (interquartile range [IQR] 5.29–6.91), which is reflective of a biologic initiation cohort.

Eighty-three percent of the cohort were biologics-naive at registration. For 74% of patients, the first biologic received during the 3-year period was a TNFi: etanercept (32%), adalimumab (20%), infliximab (17%), and certolizumab (5%). Of these patients, 88% were started on a TNFi originator. The remaining patients were prescribed either an interleukin-6 (IL-6) inhibitor (4.4%) (tocili-

zumab [4.3%] or sarilumab [0.1%]), rituximab (5.3%), or continued without receiving biologics as part of the csDMARD comparison
Patients receiving JAK inhibition or anakinra were excluded from the analyses. During the 3-year follow-up, 7,510 patients (31.8%) switched to a different biologic class. Less than 5% of the cohort (n = 1,174) were registered a second time with the BSRBR-RA and contributed more than 1 event to the analysis. Patients were asked to return a diary every 6 months during follow-up. Diaries were received from 15,205 of 23,584 patients (64.5%). Of the patients who returned a diary during the first 3 years (the exposure window for the Cox models), 63% returned more than two-thirds of the required diaries, while 16% returned fewer than one-third. Diary return was slightly lower among the IL-6 cohort and among smokers (Supplementary Table 3, http://onlinelibrary.wiley.com/doi/10.1002/art.41754/abstract).

There were 17,304 nonserious infective episodes in 8,145 patients during the 3-year follow-up period (Table 2). The median number of infections per patient was 1 (IQR 1–3). Respiratory infections accounted for 36% of all NSI. Urinary, ear, nose, and throat, and skin infections were the next most frequently reported. Nonserious opportunistic infections were reported, with herpes zoster (n = 224) and candidiasis (n = 373) being the most frequent.

Limited to the on-drug time during the first 3 years of follow-up (the exposure window for the Cox models), there were 27.0 NSI events per 100 patient-years of follow-up (95% CI 26.6–27.4) in the multiple-failure model (Table 3). Increasing age, female sex, comorbidity burden, glucocorticoid therapy, higher RA disease activity (defined by the DAS28-ESR), and greater disability (recorded by the HAQ DI) were associated with an increased risk of NSI. Compared to never smokers, current smokers had a lower risk of NSI. Patients recruited into the BSRBR-RA in more recent years also had a lower NSI risk (Table 4). Using a single-failure model, there were 12.7 events per 100 patient-years of follow-up (95% CI 12.5–12.9) in the multiple-failure model (Table 3). Increasing age, female sex, comorbidity burden, glucocorticoid therapy, higher RA disease activity (defined by the DAS28-ESR), and greater disability (recorded by the HAQ DI) were associated with an increased risk of NSI. Compared to never smokers, current smokers had a lower risk of NSI. Patients recruited into the BSRBR-RA in more recent years also had a lower NSI risk (Table 4). Using a single-failure model, there were 12.7 events per 100 patient-years of follow-up (95% CI 12.5–12.9).
per 100 patient-years of follow-up (95% CI 12.4–12.9), indicating that 12.7% of patients reported an NSI each year (Table 5).

NSI risk according to biologic treatment. The incidence rates of NSI according to biologic treatment class and within the TNFi class are shown in Table 3. Anti–IL-6 receptor (28.3 cases per 100 patient-years) and rituximab (33.6 cases per 100 patient-years) treatments were associated with a higher risk of NSI compared to TNFi (adjusted hazard ratio [HR] 1.45 [95% CI 1.29–1.63] and adjusted HR 1.28 [95% CI 1.14–1.45], respectively) (Table 4). The biologics-naive cohort receiving csDMARDs alone had a lower risk of infection compared to those receiving TNFi (19.2 cases per 100-patient years; adjusted HR 0.64 [95% CI 0.59–0.70]) (Table 4 and Figure 1). Each biologic agent was associated with a greater risk of NSI when compared to the biologics-naive cohort receiving csDMARDs alone (Supplementary Tables 4 and 5, http://onlinelibrary.wiley.com/doi/10.1002/art.41754/abstract). The single-failure Cox model demonstrated comparable estimates (Table 6). A time-varying risk of NSI was demonstrated in the multiple-failure model; compared to TNFi, the unadjusted HR of NSI with IL-6 treatment was only significant in the first 12 months of therapy, while the unadjusted HR of NSI with rituximab became significant after 12 months of therapy (Supplementary Figure 1, http://onlinelibrary.wiley.com/doi/10.1002/art.41754/abstract).

Table 5. NSI incidence rates using single-failure Cox regression model of NSI*

| Incidence rate per 100 patient-years (95% CI) | No. of infections | Follow-up, person-years |
|---------------------------------------------|------------------|------------------------|
| Total population | 12.7 (12.4–12.9) | 8,145 | 64,035 |
| Incidence rates by treatment | | | |
| csDMARD only (no biologic) | 8.0 (7.59–8.47) | 1,260 | 15,712 |
| TNFi | 14.5 (14.2–14.9) | 6,067 | 41,756 |
| Anti–IL-6R | 12.7 (11.4–14.9) | 309 | 2,429 |
| Rituximab | 13.0 (11.8–21.3) | 454 | 3,504 |
| Incidence rates by TNF treatment | | | |
| Infliximab | 17.2 (16.4–18.1) | 1,583 | 9,190 |
| Etanercept | 13.6 (13.0–14.1) | 2,472 | 18,219 |
| Adalimumab | 14.7 (14.0–15.4) | 1,764 | 12,024 |
| Certolizumab | 10.9 (9.6–12.3) | 246 | 2,259 |

* The Cox proportional hazards model allowed patients to stop or switch therapies during the 3-year period. The follow-up time (in person-years) reflects the amount of time exposed to each drug during the analysis window. See Table 3 for definitions.

Figure 1. Kaplan-Meier and Nelson-Aalen graphs from multiple-failure Cox regression models for nonserious infections. TNFi = tumor necrosis factor inhibitor; IL-6 = interleukin-6; csDMARDs = conventional synthetic disease-modifying antirheumatic drugs.
Table 6. NSI risk using single-failure Cox regression model*

| Biologic exposure (referent TNFi) | HR (95% CI) |
|-----------------------------------|-------------|
| Unadjusted                        |             |
| Anti–IL-6R                        | 0.86 (0.76–0.96)§ |
| Rituximab                         | 0.91 (0.83–1.02) |
| csDMARD only                      | 0.61 (0.57–0.65)† |
| Imputed adjusted                  |             |
| Anti–IL-6R                        | 1.34 (1.19–1.52)‡ |
| Rituximab                         | 1.08 (0.97–1.19) |
| csDMARD only                      | 0.59 (0.55–0.63)‡ |

| TNF class exposure (referent etanercept) | HR (95% CI) |
|------------------------------------------|-------------|
| Unadjusted                               |             |
| Infliximab                               | 1.28 (1.20–1.37)‡ |
| Adalimumab                               | 1.11 (1.05–1.18)† |
| Certolizumab                             | 0.72 (0.64–0.83)‡ |
| Imputed adjusted                         |             |
| Infliximab                               | 1.03 (0.97–1.10) |
| Adalimumab                               | 1.04 (0.98–1.11) |
| Certolizumab                             | 1.16 (1.01–1.33)§ |

* HR = hazard ratio (see Table 3 for other definitions).
† P < 0.01.
‡ P < 0.05.
§ P < 0.001.

Adalimumab treatment had a higher risk of NSI compared to etanercept (adjusted HR 1.11 [95% CI 1.05–1.18]). In the unadjusted model, compared to etanercept, infliximab had a higher risk of NSI while certolizumab had a lower risk, although this did not remain significant in the multivariable analysis (Table 6 and Figure 1).

Sensitivity analyses. Further analyses were performed by examining different exposures, including an on-drug time–only model and an ever-exposed model (Supplementary Table 6, http://onlinelibrary.wiley.com/doi/10.1002/art.41754/abstract) and by examining NSI risk by method of ascertainment (patient-reported, n = 8,991; consultant-reported, n = 7,375; and patient and consultant-reported, n = 930) (Supplementary Table 7, http://onlinelibrary.wiley.com/doi/10.1002/art.41754/abstract). These analyses demonstrate estimates consistent with those of the primary analysis. To account for patients who were registered a second time and contributed to more than 1 drug cohort, SEs were recalculated using the cluster-robust sandwich estimator. This made no difference to the estimated confidence intervals or P values, and thus the interpretation appears robust (Supplementary Table 8, http://onlinelibrary.wiley.com/doi/10.1002/art.41754/abstract). A competing risk survival model was used to account for the effect of serious infection in the NSI analysis. This demonstrated comparable estimates (Supplementary Table 9, http://onlinelibrary.wiley.com/doi/10.1002/art.41754/abstract).

DISCUSSION

To date, NSI have received little attention in the research literature and are an underappreciated component of disease burden in RA. In this large cohort, we have demonstrated a high frequency of NSI, affecting more than 1 in 10 patients annually. For every 100 patients, we report a rate of 27 nonserious events per year. This rate is comparable to that observed in other observational studies (12). Patients experience multiple infectious episodes, with respiratory infections being the most frequent.

The risk factors for developing an NSI are comparable to those observed in patients with serious infections (4,12,22). This includes increasing age, comorbidities, and RA disease severity. By contrast, the impact of smoking on NSI risk is distinct from what is seen with serious infections. Interestingly, being a current smoker is associated with a lower risk of NSI. It is possible that a smoker with an infection is less likely to be managed as an outpatient compared to a nonsmoker. Indeed, cigarette smoking is a significant risk factor for severe viral and bacterial infection (23) and for inpatient admission when presenting with infective symptoms (24). Smokers are susceptible to developing chronic lung disease, which is also associated with increased hospitalization, especially in the presence of infective respiratory symptoms (6,25). It is also possible that smokers underreport their infections, perhaps attributing an NSI to a chronic cough. Finally, this may be due to reporting bias as current smokers had a lower diary return rate, and we assumed that non-return indicated no infection.

There was a 5% reduction in risk of NSI for each subsequent year patients were recruited into the BSRBR-RA. The rate of infections in RA patients appears to be changing over time. This has been described with serious infectious events (26) and likely reflects shorter RA disease duration and a lower disease burden. This could be artefactual, as diary return rates have reduced in recent years.

Our findings demonstrate that biologics are likely to be associated with an increased risk of NSI. The csDMARD cohort had the lowest infection rates. There was a 40% decrease in risk of NSI with csDMARDs compared to TNFi. This is consistent with findings from the Corrona registry, in which TNFi was associated with an increased rate of outpatient infections (12). It also mirrors observations from studies examining serious infection in the BSRBR-RA (7,26) and other observational cohorts (8,9,27,28), although the magnitude of NSI risk is far greater.

Comparisons of the risk of NSI between different biologic drugs reveal similar patterns to those seen with serious infection (11). The risk was greater with rituximab compared to TNFi. IL-6 inhibition with tocilizumab therapy was also associated with a greater risk of NSI after adjusting for both patient and disease factors. It is biologically plausible that IL-6 inhibition with tocilizumab therapy was also associated with a greater risk of NSI after adjusting for both patient and disease factors. It is biologically plausible that IL-6 inhibition with tocilizumab therapy was also associated with a greater risk of NSI after adjusting for both patient and disease factors. It is biologically plausible that IL-6 inhibition with tocilizumab therapy was also associated with a greater risk of NSI after adjusting for both patient and disease factors. It is biologically plausible that IL-6 inhibition with tocilizumab therapy was also associated with a greater risk of NSI after adjusting for both patient and disease factors. It is biologically plausible that IL-6 inhibition with tocilizumab therapy was also associated with a greater risk of NSI after adjusting for both patient and disease factors.
seen in a large US multidatabase observational study, a greater risk of serious bacterial infection (HR 1.19) and of skin and soft tissue infections (HR 2.38) with tocilizumab, compared to TNFi, were reported (31). There are fewer data on NSI with tocilizumab. A high rate of NSI (40 per 100 patient-years) was reported with tocilizumab therapy in a small German RA cohort (32). Concomitant therapy with prednisolone, leflunomide, previous exposure to rituximab, and high disease activity were significant predictors of infection.

We have also demonstrated that the rates of NSI differ within the TNFi class. The highest rates were reported with infliximab and adalimumab. Compared to etanercept, adalimumab was associated with a greater risk of NSI. This differential NSI risk with the monoclonal TNFi (infliximab and adalimumab) compared to the soluble TNF receptor antagonist (etanercept) has been demonstrated previously. A meta-analysis of placebo-controlled RCTs in the treatment of immune-mediated inflammatory diseases showed the lowest number of NSI events with etanercept. The authors estimated a 20% higher risk with infliximab and adalimumab, compared to placebo, than what was observed with etanercept (14). This differential finding was also reported with herpes zoster in the German registry (33) but not in the BSRBR-RA analysis (34).

Our study has several strengths. The first is attributable to the size and quality of real-world data that the BSRBR-RA provides. There are limited missing data on baseline covariates and accurate coding of biologics. Adverse event capture data is robust, obtained from multiple sources permitting the evaluation of nonserious events. The use of TNFi rather than csDMARDs as the comparator arm allows for the comparison across biologic agents. This is more clinically relevant for physicians who are considering therapeutic options in patients who have not responded to csDMARDs. Last, the use of particular statistical models has built on decades of registry analyses, learning how to handle complex data sets with time-varying components and significant confounding.

We acknowledge several important limitations. We are unable to comment on the risk of NSI with certain agents, as few patients were registered having received these medications. This includes golimumab and abatacept, as these cohorts were never recruited to the BSRBR-RA, as well as the JAK inhibitors tofacitinib and baricitinib, which have only been recruited since 2017/2018. We cannot account for national guidelines, drug costs, and local treatment pathways, which influence decisions on medication choice.

We describe NSI as reported to the BSRBR-RA but must acknowledge that the mode of data capture for such events is inevitably incomplete and prone to misclassification bias and reporting bias. The rates of infection are likely to be underestimated, but the HRs should be unbiased as there was no differential reporting by drug. The definitions of NSI are less robust than for serious infections. As we did not require a documented antibiotic prescription, a proportion of the events may not have been of infectious etiology. Similarly, only NSI requiring antibiotics were reported by patients in their diaries, and some infectious events, such as viral infections, may not have been captured at all. It is unlikely that misclassification or missed events differs significantly across the treatment groups, as identical capturing mechanisms were employed, although there is still a risk of reporting bias between biologic agents and csDMARDs. The proportion of patients returning diaries has reduced over time, which may also introduce bias. However, a high rate of NSI was seen with IL-6 inhibition, a drug cohort recruited to the BSRBR-RA in more recent years, with a lower rate of diary return. If anything, we may be underestimating the risk of NSI with IL-6 and biasing toward the null hypothesis. Finally, despite adjusting for baseline variables that predict NSI, there is a possibility that some degree of confounding persists.

In conclusion, NSI events are common in patients with RA, with similar predictors to those observed with serious infections. An NSI history should be routinely captured in clinical practice. Biologics are associated with a greater risk of NSI, with differences in incidence and risk between treatments. These results provide clinicians with information on how to identify patients at a greater risk of NSI and guide them on the best possible treatment strategies.

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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 published. Dr. Bechman 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. Bechman, Cope, Galloway.

Acquisition of data. Bechman, the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis Contributors Group, Hyrich, Galloway.

Analysis and interpretation of data. Bechman, Halai, Yates, Norton, Hyrich, Galloway.

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APPENDIX A: PARTICIPATING INSTITUTIONS AND INVESTIGATORS IN THE BSRBR CONTROL CENTRE CONSORTIUM

The BSRBR Control Centre Consortium consists of the following institutions (all in the UK): Antrim Area Hospital, Antrim (Dr. Nicola Maiden), Cannock Chase Hospital, Cannock Chase (Dr. Tom Price), Christchurch Hospital, Christchurch (Dr. Neil Hopkinson), Derbyshire Royal Infirmary, Derby (Dr. Sheila O’Reilly), Dewsbury and District Hospital, Dewsbury (Dr. Lesley Hordon), Freeman Hospital, Newcastle-upon-Tyne (Dr. Ian Griffiths), Gartnavel General Hospital, Glasgow (Dr. Duncan Porter), Glasgow Royal Infirmary, Glasgow (Professor Hilary Capell), Haywood Hospital, Stoke-on-Trent (Dr. Andy Hassell), Hope Hospital, Salford (Dr. Romela Benitha), King’s College Hospital, London (Dr. Ernest Choy), Kings Mill Centre, Sutton-in-Ashfield (Dr. David Walsh), Leeds General Infirmary, Leeds (Professor Paul Emery), Macclesfield District General Hospital, Macclesfield (Dr. Susan Knight), Manchester Royal Infirmary, Manchester (Dr. Ian Bruce), Musgrave Park Hospital, Belfast (Dr. Allister Taggart), Norfolk and Norwich University Hospital, Norwich (Professor David Scott), Poole General Hospital, Poole (Dr. Paul Thompson), Queen Alexandra Hospital, Portsmouth (Dr. Fiona McCrae), Royal Glamorgan Hospital, Glamorgan (Dr. Rhian Goodfellow), Russells Hall Hospital, Dudley (Professor George Kitas), Selly Oak Hospital, Selly Oak (Dr. Ronald Jubb), St Helens Hospital, St Helens (Dr. Rikki Abernethy), Weston General Hospital, Weston-super-Mare (Dr. Shane Clarke/Dr. Sandra Green), Withington Hospital, Manchester (Dr. Paul Sanders), Withybush General Hospital, Haverfordwest (Dr. Amanda Coulson), North Manchester General Hospital (Dr. Bev Harrison), Royal Lancaster Infirmary (Dr. Marwan Bukhari), and the Royal Oldham Hospital (Dr. Peter Klimiuk).