RHEUMATOLOGY

Rheumatology 2021;60:2223–2230
doi:10.1093/rheumatology/keaa557
Advance Access publication 9 December 2020

Original article

Incidence, risk factors and validation of the RABBIT score for serious infections in a cohort of 1557 patients with rheumatoid arthritis

Konstantinos Thomas[1], Argyro Lazarini[1], Evripidis Kaltsonoudis[2], Paraskevi V. Voulgari[2], Alexandros A. Drosos [2], Argyro Repa[3], Ainour Molla Ismail Sali[3], Prodromos Sidiropoulos[3], Panagiota Tsatsani[4], Sousana Gazi[4], Argyriou Evangelia[5], Kyriaki A. Boki[5], Pelagia Katsimbri[1], Dimitrios Boumpas[1], Kalliopi Fragkiadaki[1], Maria G. Tektonidou [1], Petros P. Sfikakis [1], Konstantina Karagianni[6], Lazaros I. Sakkas[6], Eleftheria P. Grika[1], Panagiotis G. Vlachoyiannopoulos[1], Gerasimos Evangelatos [7], Alexios Iliopoulos[7], Theodoros Dimitroulas [8], Alexandros Garyfallos[8], Konstantinos Melissaropoulos[9], Panagiotis Georgiou[9], Maria Areti[10], Constantinos Georganas[11], Periklis Vounotrypidis[12], Georgios Georgiopoulos[1], George D. Kitas[1,13] and Dimitrios Vassilopoulos[1]

Abstract

Objectives. Predicting serious infections (SI) in patients with rheumatoid arthritis (RA) is crucial for the implementation of appropriate preventive measures. Here we aimed to identify risk factors for SI and to validate the RA Observation of Biologic Therapy (RABBIT) risk score in real-life settings.

Methods. . A multi-centre, prospective, RA cohort study in Greece. Demographics, disease characteristics, treatments and comorbidities were documented at first evaluation and one year later. The incidence of SI was recorded and compared with the expected SI rate using the RABBIT risk score.

Results. . A total of 1557 RA patients were included. During follow-up, 38 SI were recorded [incidence rate ratio (IRR): 2.3/100 patient-years]. Patients who developed SI had longer disease duration, higher HAQ at first evaluation and were more likely to have a history of previous SI, chronic lung disease, cardiovascular disease and chronic kidney disease. By multivariate analysis, longer disease duration (IRR: 1.05; 95% CI: 1.005, 1.1), history of previous SI (IRR: 4.15; 95% CI: 1.7, 10.1), diabetes (IRR: 2.55; 95% CI: 1.06, 6.14), chronic lung disease (IRR: 3.14; 95% CI: 1.35, 7.27) and daily prednisolone dose $\geq$10 mg (IRR: 4.77; 95% CI: 1.47, 15.5) were independent risk factors for SI. Using the RABBIT risk score in 1359 patients, the expected SI incidence rate was 1.71/100 patient-years, not different from the observed (1.91/100 patient-years; $P = 0.97$).

Conclusion. In this large real-life, prospective study of RA patients, the incidence of SI was 2.3/100 patient-years. Longer disease duration, history of previous SI, comorbidities and high glucocorticoid dose were independently associated with SI. The RABBIT score accurately predicted SI in our cohort.

Key words: rheumatoid arthritis, infections, comorbidities, glucocorticoids, risk score

[1]Joint Rheumatology Program, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece, [2]Rheumatology Clinic, University of Ioannina, Ioannina, Greece[3]Clinical Immunology and Allergy Department, University of Crete, Heraklion, Greece, [4]Rheumatology Unit, KAT Hospital, Athens, Greece, [5]Rheumatology Unit, Sismanoglio Hospital, Athens, Greece, [6]Department of Rheumatology, University of Thessaly, Larissa, Greece, [7]Rheumatology Unit, NIMTS Hospital, Athens, Greece, [8]4th Department of Medicine, Aristotle University, Thessaloniki, Greece, [9]Rheumatology Unit, Agios Andreas Hospital, Patras, Greece, [10]Private Practice, Leivadia, Greece, [11]Private Practice, Athens, Greece, [12]Private Practice, Thessaloniki, Greece and [13]Rheumatology Department, Hygeia Hospital, Athens, Greece

Submitted 19 May 2020; accepted 3 August 2020

Correspondence to: Dimitrios Vassilopoulos, Joint Rheumatology Program, Clinical Immunology-Rheumatology Unit, 2nd Department of Medicine and Laboratory, National and Kapodistrian University of Athens, School of Medicine, Hippokration General Hospital, 114 Vass. Sophias Ave., 115 27 Athens, Greece. E-mail: dvassilop@med.uoa.gr

Rheumatology key messages

- In this contemporary RA cohort, incidence of serious infections was 2.3 per 100 patient-years.
- Disease characteristics, comorbidities and glucocorticoids rather than bDMARDs were associated with serious infections.
- RABBIT score was well balanced in predicting the infection risk in our cohort.

Introduction

Serious infections (SI) are still one of the most common and severe comorbidities of RA in the modern era of biologic and targeted synthetic disease-modifying antirheumatic drugs (b and tsDMARDs), associated with significant morbidity and mortality [1–5]. Data from real-world registries have identified several factors associated with SI risk including active disease, functional impairment, type of antirheumatic treatment and certain comorbidities. The timely and accurate recognition of patients at high risk for SI could be beneficial in many ways, such as applying the necessary preventive measures (e.g. up-to-date immunizations, infection prevention and control training) [6, 7], avoiding or modifying treatments that pose an increased risk for infection and educating the patients to promptly identify the early signs of a SI [8].

So far a number of risk scores for accurate prediction of SI from US [1, 9] and European [2] RA cohorts have been proposed but not independently validated in other real-life RA cohorts. The most recent of these was the RABBIT risk score, derived from the German Biologics RA registry [2, 10].

In this prospective, multi-centre, real-life, cohort study, our goals were to estimate the incidence and risk factors for SI as well as to validate the RABBIT risk score in our patient population.

Methods

Patients and study design

This was a multi-centre, prospective, cohort study by the RA Study Group of the Greek Rheumatology Society [11]. Inclusion criteria included age $\geq$18 years and RA diagnosis according to ACR/EULAR classification criteria [12]. During the first cross-sectional evaluation, data on patient and disease characteristics, treatment patterns and comorbidities were collected. More details about the study design have been published [11].

The patients were re-evaluated 1 year later and their disease characteristics (Disease Activity Score using 28 joints—DAS28-ESR, HAQ), treatment patterns and serious events that occurred during that period (SI, arthroplasties, cardiovascular events, hospitalization for any reason, osteoporotic fractures, neoplasms) were recorded. Data were collected either through a printed case-reporting form or via a web-based form (www.rheumstudygrps.gr) at both evaluations.

Institutional Review Board approval was provided by the Joint Rheumatology Program (Hippokration General Hospital as the co-ordinating centre, 64/16–4-2015 and 7/23–3-2016) and by the local institutional boards of participating centres. All patients provided written informed consent at first evaluation.

RABBIT risk score

SI, defined as those requiring hospitalization or intravenous antibiotics as well as opportunistic infections (bacterial, viral or parasitic, such as herpes zoster-HZ or tuberculosis), were recorded for the entire patient population ($n = 1557$). For patients with available data ($n = 1359$), the expected likelihood of SI was calculated using the RA Observation of Biologic Therapy (RABBIT) risk score as previously described [2, 10].

Statistical analysis

A χ^2 test was used for comparison of categorical variables and *t* test for continuous variables with normal distribution or Mann–Whitney for those non-normally distributed. Incidence of the main outcome (i.e. SI) was modelled and analysed with generalized linear models (Poisson family with log link) in view of the rarity of events (35 out of 1557) and previously published data [2, 10]. In addition, we sought to account for the potential impact of dropouts and treatment changes during follow-up on the robustness of our results by employing inverse probability weighted regression adjustment. In brief, we used probit regression on the treatment outcome (patient status with respect to SI available or lost at the end of the follow-up) including a pre-specified set of covariates [age, sex, educational level, working status, disease duration, DAS28-ESR, HAQ, bDMARDs, combination of cs- (conventional synthetic) and bDMARDs, glucocorticoids (GCs) and Rheumatic Disease Comorbidity Index (RDCI)] and calculated predicted conditional probabilities for each participant. Subsequently, we generated inverse probability weights separately for subjects with full duration of follow-up and those lost before completion of the study. Finally, we fitted the generalized linear models with the inverse probability weights and robust standard errors to estimate unbiased treated effects.

We implemented two discrete generalized linear models:

- a model with the validated RABBIT score as a single predictor;

- a multivariable model adjusting for a predefined set of covariates, including age, previous history of SI, disease duration, HAQ, GCs, diabetes, chronic lung disease, chronic kidney disease (CKD), cardiovascular disease, treatment with bDMARDs. Those variables were selected based on biological plausibility and previous literature. To avoid overfitting due to the low ratio of events to predictors, we performed bootstrapping with 500 replicates and calculated bootstrapped 95% CI around the mean estimate.

Effect estimates are displayed as incidence rate ratios (IRR) and their respective 95% CI.

We confirmed satisfactory fit of the RABBIT risk score in our cohort by using the Hosmer-Lemeshow goodness-of-fit test with 10 groups. Further, we generated a bar plot with predicted probabilities derived from generalized weight-adjusted linear regression score of SI on the RABBIT score and the observed SI incidence rates in each decile.

All statistical tests were two-sided and a P-value < 0.05 was considered statistically significant. All statistical analyses were performed with SPSS (IBM SPSS Statistics for Windows, Version 25.0., IBM Corp., Armonk, NY), and Stata 13 (StataCorp) software.

Results

Baseline patient characteristics

Among 2491 patients initially evaluated, 1557 (62.5%) were re-evaluated ~1 year later [mean (S.D.) interval: 13 (3.5) months]. With the exception of the more frequent use of bDMARDs (45% *vs* 35%), dyslipidaemia (35% *vs* 30%) and less frequent use of GCs (37% *vs* 45%), no other significant differences were noted between those with both evaluations ($n = 1557$) and those with only the first evaluation available ($n = 934$, see Supplementary Table S1, available at *Rheumatology* online).

The patient characteristics at first evaluation are shown in Table 1. The vast majority of patients were on DMARDs at first evaluation: csDMARD monotherapy: 48.6%, cs- and bDMARD combination: 34.6%, bDMARD monotherapy: 11.7%. Among csDMARDs, methotrexate was the most commonly used (77.7%) followed by leflunomide (17.2%) and hydroxychloroquine (15.6%). Approximately 40% of patients were on GCs at a mean daily prednisolone dose of 4.9 mg.

Rate of serious infections

During 1663 patient-years of follow-up, 38 infections were recorded in 35 patients (IRR: 2.3/100 patient-years). Respiratory tract infections were the most common (50%), followed by HZ infection (13%, 0.3/100 patient-years), pyelonephritis (11%) and acute bacterial skin and skin structure infections (11%, Table 2).

Among the 8 deaths that occurred during follow-up (0.51%), 3 were due to SI and all of them involved the respiratory tract. There was only 1 case of tuberculosis recorded (IRR: 0.06/100 patient-years).

Risk factors for serious infections

The group of patients who developed SI ($n = 35$) had longer disease duration, higher baseline HAQ, more frequent history of prior SI and were more likely to be treated with GCs and have certain comorbidities such as diabetes mellitus, chronic pulmonary disease, cardiovascular disease and CKD (defined as stages 3–5: estimated glomerular filtration rate <30 ml/min/1.73m^2) compared with those who did not ($n = 1522$, Table 3).

By Poisson weight-adjusted regression, history of previous SI (IRR = 4.15; 95% CI: 1.7, 10.1), daily prednisolone dose >10 mg (IRR = 4.77; 95% CI: 1.47, 15.5), disease duration (IRR = 1.05 per year; 95% CI: 1.005, 1.1), diabetes mellitus (IRR = 2.55; 95% CI: 1.06, 6.14) and chronic lung disease (IRR = 3.13; 95% CI: 1.35, 7.27) were independently associated with the development of SI (Table 4). Those variables remained significantly associated with the incidence of SI after bootstrapping (data not shown). The predefined multivariable model predicted a mean incidence rate of 1.63/100 patient-years and an average number of 22 SI. Resampling with 500 replicates confirmed the moderate to satisfactory predictive value of our multivariable model [mean number of events 22 (95% CI: 13, 32) and mean incidence rate 1.63 (95% CI: 0.93, 2.4)].

Role of therapies in SI risk

As shown in Supplementary Table S2, available at *Rheumatology* online, the incidence rate of SI in csDMARD-only users was 1.4/100 patient-years whereas the respective rate for those who were on bDMARDs at both evaluations (chronic users) was slightly higher at 2/100 patient-years (IRR compared with csDMARD-only users: 1.36; $P = 0.45$). This risk was higher for patients who started bDMARDs for the first time (bDMARD initiators: 3.7/100 patient-years) but the difference from csDMARD users was not statistically significant (IRR = 2.56; $P = 0.08$).

Calculation and validation of the RABBIT risk score

Among the cohort of 1557 patients, data were available for RABBIT risk score calculation in 1359 (87.3%). During 1514 patient-years of follow-up, we observed 29 SI (1.91/100 patient-years), while the expected number by the RABBIT risk score under generalized weight-adjusted linear regression score was 26.1 SI (rate: 1.71/100 patient-years). RABBIT risk score was well calibrated in our cohort with good accordance between observed and expected probabilities (Hosmer-Lemeshow chi$^2 = 2.42$; $P = 0.97$, Fig. 1). Then, we divided the expected risk to deciles and calculated the SI incidence for each subgroup. A modest to good correlation between the mean expected and observed SI incidence rate per 100 patient-years was observed (Fig. 1).

Table 1 Patient and disease characteristics at the first evaluation ($n = 1557$)

Characteristics	*n* with data available	
n		1557
Female, *n* (%)	1557	1210 (78%)
Age, years, mean (S.D.)	1557	62.9 (12.6)
Disease characteristics		
Disease duration, years, mean (S.D.)	1422	10.3 (8.9)
Seropositivity (RF and/or anti-CCP), *n* (%)	1492	799 (53.6%)
Erosions, *n* (%)	1237	543 (43.9%)
DAS28-ESR, mean (S.D.)	1380	3.37 (1.29)
HAQ, median (IQR)	1377	0.3 (0–0.88)
History of arthroplasties, *n* (%)	1557	150 (9.6%)
Treatment		
csDMARDs, *n* (%)	1557	1295 (83.2%)
csDMARD monotherapy		756 (48.6%)
bDMARDs, *n* (%)	1557	721 (46.3%)
TNFi		379 (53%)
nonTNFi		342 (47%)
bDMARD monotherapy		182 (11.7%
Combination therapy (cs and bDMARDs)	1557	539 (34.6%)
Glucocorticoids, *n* (%)	1557	628 (40.3%)
Prednisolone daily dose, mean (S.D.)	614	4.9 (3.6) mg
Comorbidities		
Smoking, current/past	1491	278 (18.6%)/243 (16.3%)
Obesity (BMI $\geq$ 30 kg/m^2)	1337	346 (26%)
Hypertension	1557	669 (43%)
Dyslipidemia	1557	535 (34.4%)
Osteoporosis	1557	441 (28.3%)
Diabetes	1557	220 (14.1%)
Depression	1557	200 (12.8%)
Coronary artery disease	1557	92 (5.9 %)
Chronic lung disease	1557	155 (10%)
COPD		94 (6%)
RA-associated ILD		80 (5.1%)
Cancer, current/past	1557	19 (1.2%)/ 82 (5.3%)
CKD (stages 3–5)	1501	14 (0.9%)
Peripheral artery disease	1557	70 (4.5%)
Stroke	1557	46 (3%)
RDCI, median (IQR)	1557	1 (0–2)

anti-CCP, anti-cyclic citrullinated peptide antibodies; DAS28, Disease Activity Score using 28 joints; IQR, interquartile range; csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; bDMARDs, biologic DMARDs; CKD, chronic kidney disease; RDCI, Rheumatic Disease Comorbidity Index.

Discussion

In this large, real-life, RA cohort the incidence of SI was 2.3/100 patient-years. Certain factors such as long disease duration, history of previous SI, chronic lung or kidney disease as well as high daily GC dose were identified as independent predictors for SI. The RABBIT risk score accurately predicted the likelihood of SI in our patient cohort.

Our RA cohort had certain unique characteristics. The majority of patients had long-standing, established disease, approximately half were older than 65 years and their comorbidity burden was higher compared with other RA cohorts [13, 14] whereas almost half of them were on bDMARDs. Conversely, RA was relatively well controlled as illustrated by their low DAS28-ESR and HAQ scores. Overall, the SI incidence rate was 2.3/100 patient-years, which is similar to the rates reported in other international [15], US (1.9/100 patient-years) [16], German (1.8–3/100 patient-years) [2] and Greek (2.1–4/100 patient-years) [17, 18] real-life registries.

By multivariate analysis, disease duration (but not age), history of previous SI, chronic lung or kidney disease and high prednisolone dose ($\geq$10 mg/day) were independently associated with SI.

The contributory role of GCs in SI risk in RA patients is well established [2, 10, 19–21]. In our cohort, patients treated with $\geq$10 mg of prednisolone a day, had a 6-times higher risk for SI compared with those treated

with <10 mg/day. It should be emphasized though that the proportion of patients receiving such a high dose was very small (3%) while only 24% were on >5 mg/day.

The use of b- or csDMARDs was not identified as an independent risk factor for SI in our cohort. Although the SI incidence among bDMARD chronic users (2.0/100 patient-years) or initiators (3.7/100 patient-years) was higher compared with csDMARD-only users (1.4/100 patient-years), this difference was not statistically significant. The SI rate of our bDMARD starters (3.7/100 patient-years) was slightly lower than that reported in the British Registry (5.51/100 patient-years) [22].

Chronic lung disease [defined as the presence of chronic obstructive pulmonary disease (COPD) and/or RA-associated interstitial lung disease (ILD)] was present in ~10% of patients and it was associated with a 3-fold increased risk for SI. Apart from the well-known predisposition to infections for all COPD stages [23], it has also been shown that RA-related ILD is associated with a higher SI risk (especially pneumonia) [24]. These findings emphasize the need for universal vaccination (with the flu and pneumococcal vaccines) and close monitoring of RA patients with underlying chronic lung disease [6, 25].

History of previous SI should sound an alarm for both patients and physicians, as we found that such patients had a 4-times higher risk for developing a new SI. Our findings are in accordance with similar findings from other real-life cohorts [1, 2, 10, 26–29] indicating that such history is probably the most significant factor in determining future SI risk in RA patients.

Opportunistic infections such as tuberculosis and HZ were uncommon [30]. There was only 1 case of tuberculosis corresponding to an incidence of 0.06/100 patient-years, a rate that is comparable to that seen in low-prevalence countries after the implementation of universal screening for latent tuberculosis infection before bDMARD initiation [31]. Regarding HZ, the crude incidence was 0.3/100 patient-years, which was slightly lower than that reported in the British (0.7–1.6/100 patient-years) [32] and the US Corrona (0.7–1/100 patient-years) [33] registries.

A number of risk scores for predicting SI in RA patients have been proposed [1, 2, 9] Crowson *et al.* identified and included in their risk assessment model the following variables: age, prior SI, extra-articular RA, ESR, GC dose and the number of comorbidities [1]. Although it shares common variables with the RABBIT score, this risk score was based on a cohort diagnosed

Table 2 Type and frequency of serious infections

Site of infection	*n* (%)
Respiratory	19 (50%)
Herpes zoster	5 (13%)
Pyelonephritis	4 (11%)
Acute bacterial skin and skin structure infections	4 (11%)
Other	
Gastrointestinal tract	2 (5%)
Central nervous system	1 (2.5%)
Pulmonary tuberculosis	1 (2.5%)
Spondylodiskitis	1 (2.5%)
Herpetic stomatitis	1 (2.5%)

Table 3 Comparison between patients who developed ($n = 35$) or not ($n = 1522$) serious infections

Variable	SI (−) $n = 1522$	SI (+) $n = 35$	*P*-value*
Female, *n* (%)	1.186 (78.2%)	24 (68.6%)	0.17
Age, years, mean (S.D.)	62.8 (12.6)	66.4 (10.9)	0.1
Disease duration, years, mean (S.D.)	**10.2 (8.9)**	**14.1 (10.3)**	**0.014**
DAS28-ESR, mean (S.D.)	3.36 (1.29)	3.69 (1.31)	0.17
HAQ, mean (S.D.)	**0.50 (0.66)**	**0.88 (0.87)**	**0.002**
History of serious infection, *n* (%)	**147 (9.2%)**	**12 (34.3%)**	**<0.001**
Arthroplasties, *n* (%)	144 (9.5%)	6 (17.1%)	0.13
Glucocorticoids, *n* (%)	**607 (39.9%)**	**21 (60%)**	**0.016**
Prednisolone ≥10 mg/day, *n* (%)	44 (2.9%)	3 (8.6%)	0.053
Prednisolone, daily dose, mean (S.D.)	4.9 (3.6) mg	5.1 (4.1) mg	0.8
bDMARDs, *n* (%)	704 (46.3%)	17 (48.6%)	0.78
Diabetes mellitus, *n* (%)	**211 (13.9%)**	**9 (25.7%)**	**0.047**
Chronic lung disease, *n* (%)	**145 (9.5%)**	**10 (28.6%)**	**<0.001**
Cardiovascular disease, *n* (%)	**175 (11.5%)**	**8 (22.9%)**	**0.039**
CKD, stages 3–5, *n* (%)	**12 (0.8%)**	**2 (6.1%)**	**0.002**
BMI, kg/m^2, mean (S.D.)	27.5 (5.0)	28.7 (6.3)	0.2
RDCI, mean (S.D.)	**1.12 (1.2)**	**1.97 (1.6)**	**0.001**

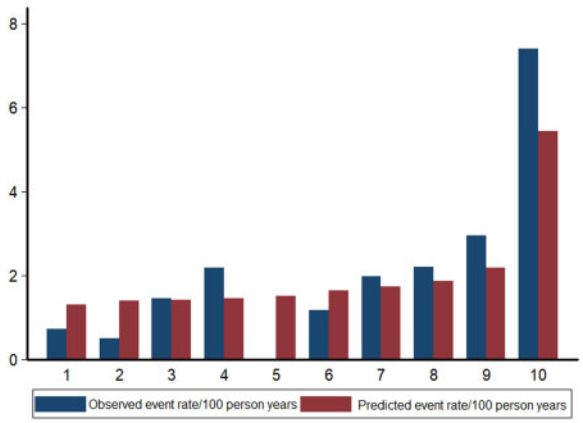
*Statistically significant differences ($P < 0.05$) between groups are shown in bold. SI, serious infections; anti-CCP, anti-cyclic citrullinated peptide antibodies; DAS28, Disease Activity Score using 28 joints; IQR, interquartile range; csDMARDs, conventional synthetic disease modifying anti-rheumatic drugs; bDMARDs, biologic DMARDs; CKD, chronic kidney disease; RDCI, Rheumatic Disease Comorbidity Index.

Table 4 Uni- and multivariate logistic regression analysis of factors associated with serious infections

Variable	Univariate		Multivariate	
	IRR (95% CI)	*P*	IRR (95% CI)	*P*-value*
Age	1.04 (1.003, 1.087)	0.034	1.007 (0.96, 1.05)	0.72
Disease duration	1.05 (1.01, 1.09)	0.01	**1.05 (1.003, 1.1)**	**0.018**
Baseline HAQ	1.46 (1.07, 2.00)	0.018	1.09 (0.58, 2.08)	0.77
History of serious infection	6.52 (2.75, 15.5)	<0.001	**4.15 (1.70, 10.12)**	**0.002**
Prednisolone ≥10 mg/day *vs* <10 mg/day	3.49 (0.83, 14.65)	0.09	**4.77 (1.47, 15.5)**	**0.009**
bDMARD use	1.10 (0.47, 2.59)	0.81	0.83 (0.32, 2.18)	0.71
Diabetes mellitus	3.67 (1.49, 9.01)	0.005	**2.55 (1.06, 6.14)**	**0.036**
Chronic lung disease	5.87 (2.41, 14.27)	<0.001	**3.13 (1.35, 7.27)**	**0.008**
Cardiovascular disease	4.31 (1.76, 10.58)	0.001	2.06 (0.70, 6.08)	0.19
CKD (stage 3–5 *vs* 0–2)	6.58 (0.98, 44.16)	0.052	3.20 (0.77, 13.31)	0.11

*Variables with statistically significant differences ($P < 0.05$) between groups by multivariate analysis are shown in bold. IRR, incidence rate ratio; bDMARD, biologic disease-modifying anti-rheumatic drug; CKD, chronic kidney disease.

Fig. 1 Bar plot of observed and predicted probabilities for serious infections by the RABBIT risk score



between 1955 and 1994 with significantly higher SI incidence, well before the introduction of biologics in clinical practice. Curtis *et al.* [9] published two separate risk scores for SI using governmental and commercial insurance data, respectively. They constructed these scores based on age, comorbidities and daily prednisone dose (≤ or >7.5 mg). The derivation cohorts of this study had some unique characteristics that may also preclude the generalization of the results. First, the risk score creation was based on patients not treated with bDMARDs. Second, both cohorts were quite different in terms of age and the prevalence of comorbidities compared with ours and this is also depicted in their SI incidence rates. Third, among the beneficiaries of the governmental insurance cohort almost 30% were receiving subsidies for reasons other than age.

The RABBIT score was the latest to be developed based on data from the German Registry of Biologics [2]. The variables included in the final score were age (< or > 60 years), functional status, specific comorbidities (chronic lung or kidney disease), treatment with GCs (≤7.5 mg/day, 7.5–15 mg/day or above), number of previous DMARD treatment failures, current treatment [TNF inhibitors (TNFi), other bDMARDs or csDMARDs] and previous SI.

In our cohort, in contrast to the German Registry Cohort [2, 10], treatment characteristics (previous DMARD failures or type of current DMARD therapy) or age were not identified as independent risk factors for SI. It should be noted though, that in the study by Zink *et al.* [2] patients were included at the initiation of a TNFi or a csDMARD, whereas in our study RA patients who were starting or had been on any type of biologic or non-biologic DMARD were enrolled and prospectively followed for 1 year. Despite these differences, after applying the appropriate methods, we found that RABBIT score was well balanced in predicting the SI risk across the total range of risk. This is a novel finding, since to our knowledge, this is the first study in the literature that independently validated this score in a large population of patients with established RA treated with biologic and non-biologic DMARDs.

The strengths of our study include its multi-centre and prospective design, the participation of referral centres with established experience in the care of RA patients, the large number of included patients, the multiple collected parameters allowing adjustment for and elimination of the effects of potential confounders and the inclusion of patients receiving cs- as well as bDMARDs.

Our study also has certain limitations. First, loss to follow-up occurred in 37.5% of the patients registered at first evaluation. Without doubt, this could have affected the number of observed SI if we consider that the missing patients had a significantly lower or higher SI rate. However, loss to follow-up is not rare in real-world registries [34] and no significant differences between those with or without available data at second

evaluation were noted. Second, we cannot preclude that some of the SI, especially HZ cases, were not captured and have been managed by primary care physicians or other specialties. However, we believe that this is not the case, since rheumatologists in Greece are usually responsible for the holistic care of patients with RA. Finally, our cohort consisted mainly of patients with long-standing disease who were primarily registered from tertiary referral centres. Nevertheless, we have previously shown that their characteristics are similar to the general RA population in Greece as they were captured by the obligatory, nationwide, electronic prescription system [11, 35].

In conclusion, we have identified certain risk factors for SI in patients with established RA in real-life settings. Risk stratification is a prerequisite for preventing SI in RA patients, especially in the era of newly introduced therapies such as the tsDMARDs (JAK inhibitors) [36]. In that direction, the availability of reliable tools for predicting SI could be very informative and useful. In this study, we validated the RABBIT risk score as a reliable predictive tool for SI in daily clinical practice.

Thus, in RA patients who are identified as high risk for SI by easy-to-use tools, implementation of preventive measures such as reducing GC exposure, implementing universal vaccination coverage for influenza, pneumococcus and HZ, and promoting awareness among rheumatologists and patients for early signs of infection, could further reduce this risk.

Funding: The study was funded by the Greek Rheumatology Society and the Professional Association of Greek Rheumatologists and by the Special Account for Research Grants (S.A.R.G.), National and Kapodistrian University of Athens, Athens, Greece (DV, Grants #12085, 12881).

Disclosure statement: The authors have declared no conflicts of interest.

Supplementary data

Supplementary data are available at *Rheumatology* online.

References

1 Crowson CS, Hoganson DD, Fitz-Gibbon PD, Matteson EL. Development and validation of a risk score for serious infection in patients with rheumatoid arthritis. Arthritis Rheum 2012;64:2847–55.

2 Zink A, Manger B, Kaufmann J *et al.* Evaluation of the RABBIT risk score for serious infections. Ann Rheum Dis 2014;73:1673–6.

3 Singh JA, Cameron C, Noorbaloochi S *et al.* Risk of serious infection in biological treatment of patients with rheumatoid arthritis: a systematic review and meta-analysis. Lancet 2015;386:258–65.

4 Ogdie A, Maliha S, Shin D *et al.* Cause-specific mortality in patients with psoriatic arthritis and rheumatoid arthritis. Rheumatology (Oxford) 2017;56:907–11.

5 Young A, Koduri G, Batley M *et al.* Mortality in rheumatoid arthritis. Increased in the early course of disease, in ischaemic heart disease and in pulmonary fibrosis. Rheumatology (Oxford) 2006;46:350–7.

6 Furer V, Rondaan C, Heijstek MW *et al.* 2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis 2020;79:39–52.

7 Adami G, Fassio A, Orsolini G *et al.* Effectiveness of influenza vaccine in TNF inhibitors treated patients: comment on the article by Burmester et al. Ann Rheum Dis 2019, doi: 10.1136/annrheumdis-2019-215174.

8 Seymour CW, Gesten F, Prescott HC *et al.* Time to treatment and mortality during mandated emergency care for sepsis. N Engl J Med 2017;376:2235–44.

9 Curtis JR, Xie F, Chen L *et al.* Use of a disease risk score to compare serious infections associated with anti-tumor necrosis factor therapy among high- versus lower-risk rheumatoid arthritis patients. Arthritis Care Res (Hoboken) 2012;64:1480–9.

10 Strangfeld A, Eveslage M, Schneider M *et al.* Treatment benefit or survival of the fittest: what drives the time-dependent decrease in serious infection rates under TNF inhibition and what does this imply for the individual patient? Ann Rheum Dis 2011;70:1914–20.

11 Thomas K, Lazarini A, Kaltsonoudis E *et al.* Multicenter cross-sectional study of patients with rheumatoid arthritis in Greece: results from a cohort of 2.491 patients. Mediterr J Rheumatol 2018;29:27–37.

12 Aletaha D, Neogi T, Silman AJ *et al.* 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010;69:1580–8.

13 Dougados M, Soubrier M, Antunez A *et al.* Prevalence of comorbidities in rheumatoid arthritis and evaluation of their monitoring: results of an international, cross-sectional study (COMORA). Ann Rheum Dis 2014;73:62–8.

14 Pappas DA, Nyberg F, Kremer JM *et al.* Prevalence of cardiovascular disease and major risk factors in patients with rheumatoid arthritis: a multinational cross-sectional study. Clin Rheumatol 2018;37:2331–40.

15 Yamanaka H, Askling J, Berglind N *et al.* Infection rates in patients from five rheumatoid arthritis (RA) registries: contextualising an RA clinical trial programme. RMD Open 2017;3:e000498.

16 Mehta B, Pedro S, Ozen G *et al.* Serious infection risk in rheumatoid arthritis compared with non-inflammatory rheumatic and musculoskeletal diseases: a US national cohort study. RMD Open 2019;5:e000935.

17 Flouri I, Markatseli TE, Voulgari PV *et al.* Comparative effectiveness and survival of infliximab, adalimumab, and etanercept for rheumatoid arthritis patients in the Hellenic Registry of Biologics: low rates of remission and 5-year drug survival. Semin Arthritis Rheum 2014;43:447–57.

18 Vassilopoulos D, Delicha EM, Settas L *et al.* Safety profile of repeated rituximab cycles in unselected rheumatoid arthritis patients: a long-term, prospective real-life study. Clin Exp Rheumatol 2016;34:893–900.

19 Wolfe F, Caplan L, Michaud K. Treatment for rheumatoid arthritis and the risk of hospitalization for pneumonia: associations with prednisone, disease-modifying antirheumatic drugs, and anti-tumor necrosis factor therapy. Arthritis Rheum 2006;54:628–34.

20 Ozen G, Pedro S, England BR *et al.* Risk of serious infection in patients with rheumatoid arthritis treated with biologic versus nonbiologic disease-modifying antirheumatic drugs. ACR Open Rheumatol 2019;1:424–32.

21 Widdifield J, Bernatsky S, Paterson JM *et al.* Serious infections in a population-based cohort of 86,039 seniors with rheumatoid arthritis. Arthritis Care Res (Hoboken) 2013;65:353–61.

22 Rutherford AI, Subesinghe S, Hyrich KL, Galloway JB. Serious infection across biologic-treated patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. Ann Rheum Dis 2018;77:905–10.

23 Benfield T, Lange P, Vestbo J. COPD stage and risk of hospitalization for infectious disease. Chest 2008;134: 46–53.

24 Izumi Y, Akazawa M, Akeda Y *et al.* The 23-valent pneumococcal polysaccharide vaccine in patients with rheumatoid arthritis: a double-blinded, randomized, placebo-controlled trial. Arthritis Res Ther 2017;19:15.

25 Thomas K, Vassilopoulos D. Immunization in patients with inflammatory rheumatic diseases. Best Pract Res Clin Rheumatol 2016;30:946–63.

26 Subesinghe S, Rutherford AI, Byng-Maddick R, Hyrich KL, Galloway JB. Biologic prescribing decisions following serious infection: results from the British Society for Rheumatology Biologics Register-Rheumatoid Arthritis. Rheumatology (Oxford) 2018;57: 2096–100.

27 Accortt NA, Bonafede MM, Collier DH, Iles J, Curtis JR. Risk of subsequent infection among patients receiving tumor necrosis factor inhibitors and other disease-modifying antirheumatic drugs. Arthritis Rheumatol 2016; 68:67–76.

28 Yun H, Xie F, Delzell E *et al.* Risk of hospitalised infection in rheumatoid arthritis patients receiving biologics following a previous infection while on treatment with anti-TNF therapy. Ann Rheum Dis 2015; 74:1065–71.

29 Subesinghe S, Rutherford AI, Byng-Maddick R, Leanne Hyrich K, Benjamin GJ. Recurrent serious infections in patients with rheumatoid arthritis—results from the British Society for Rheumatology Biologics Register. Rheumatology (Oxford) 2018;57:651–5.

30 Winthrop KL, Novosad SA, Baddley JW *et al.* Opportunistic infections and biologic therapies in immune-mediated inflammatory diseases: consensus recommendations for infection reporting during clinical trials and postmarketing surveillance. Ann Rheum Dis 2015;74:2107–16.

31 Winthrop KL, Park SH, Gul A *et al.* Tuberculosis and other opportunistic infections in tofacitinib-treated patients with rheumatoid arthritis. Ann Rheum Dis 2016; 75:1133–8.

32 Galloway JB, Mercer LK, Moseley A *et al.* Risk of skin and soft tissue infections (including shingles) in patients exposed to anti-tumour necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. Ann Rheum Dis 2013;72:229–34.

33 Pappas DA, Hooper MM, Kremer JM *et al.* Herpes zoster reactivation in patients with rheumatoid arthritis: analysis of disease characteristics and disease-modifying antirheumatic drugs. Arthritis Care Res (Hoboken) 2015;67:1671–8.

34 Tien Y-C, Chiu Y-M, Liu M-P. Frequency of lost to follow-up and associated factors for patients with rheumatic diseases. PLoS One 2016;11: e0150816.

35 Sfikakis PP, Bournia VK, Sidiropoulos P. Biologic treatment for rheumatic disease: real-world big data analysis from the Greek country-wide prescription database. Clin Exp Rheumatol 2017;35:579–85.

36 Jani M, Barton A, Hyrich K. Prediction of infection risk in rheumatoid arthritis patients treated with biologics: are we any closer to risk stratification? Curr Opin Rheumatol 2019;31:285–92.