ORIGINAL ARTICLES

Severe infections in Portuguese patients with rheumatoid arthritis under biologic treatment – a multicenter, nationwide study (SIPPRA-B Study)

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ABSTRACT

Introduction: Despite years of experience with biological disease modifying anti-rheumatic drugs (bDMARD) in rheumatoid arthritis (RA), little is known about differences in infectious risk among bDMARDs. The aim of this study was to assess the incidence and type of infections in RA patients on bDMARDs and to determine possible predictors.

Methods: A retrospective multicenter cohort study that included patients registered in the Rheumatic Diseases Portuguese Registry (Reuma.pt) with RA, and exposed to at least one bDMARD until April 2021. RA patients under bDMARD and with at least one episode of severe infection (SI), defined as infection that requires hospitalization, use of parenteral antibiotics or that resulted in death, were compared to patients with no report of SI. Demographic and clinical data at baseline and at the time of each SI were collected to establish comparisons between different groups of bDMARDs. Comparisons between different bDMARDs were assessed and logistic regression was performed to identify predictors of SI.

Results: We included 3394 patients, 2833 (83.5%) female, with a mean age at RA diagnosis of 45.5±13.7 years. SI was diagnosed in 142 of the 3394 patients evaluated (4.2%), totaling 151 episodes of SI. At baseline, patients with SI had a significantly higher proportion of prior orthopedic surgery, asthma, interstitial lung disease, chronic kidney disease and corticosteroid use, higher mean age and longer median disease duration at first bDMARD. Nine patients died (6.0%). Ninety-two SI (60.9%) occurred with the first bDMARD, the majority leading to discontinuation of the bDMARD within 6 months (n=75, 49.7%), while 65 (43.0%) restarted the same bDMARD and 11 (7.3%) switched to another bDMARD (6 of them to a different mechanism of action). In the multivariable analysis, we found that chronic kidney disease, asthma, infliximab, corticosteroid use, interstitial lung disease, previous orthopedic surgery, higher Health Assessment Questionnaire and DAS284V-ESR are independent predictors of SI.

Conclusion: This study described the incidence and types of SI among Portuguese RA patients on biologics, identifying several predictors of SI, both globally and with different bDMARDs. Physicians should be aware of the real-word infectious risk in RA patients on bDMARDs when making treatment decisions.

Keywords: Rheumatoid arthritis; Immunosuppressants; Biological therapies; DMARDs.

INTRODUCTION

Rheumatoid arthritis (RA) is the most common autoimmune inflammatory arthritis in adults[1]. Several therapies have been introduced as options to the treatment of RA, namely conventional synthetic disease-modifying antirheumatic drugs (cDMARDs), and more recently the advent of biologic therapies[2-4]. Biological

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disease modifying antirheumatic drugs (bDMARDs) are a safe and effective option for the treatment of RA, as they allow a more targeted approach to treating RA,[4] but severe infections (SI) have been reported across different studies and national registries[2]. The risk of SI is not only related to the disease itself, but also to the immunomodulatory treatments used to control the disease[5]. As studies showed that efficacy does not differ significantly between the several available treatment options, safety can play a decisive role in the choice of treatment[3]. Clinical trials report safety data, but safety data derived from real-world long-term evidence are crucial to the knowledge of how these therapies behave in everyday practice[3,4].

Severe infections are defined in the literature as those that require hospitalization, treatment with parenteral antimicrobial therapy, or result in death[2,4,6]. The first observational studies detailing infectious risk in RA emerged with anti-TNFα drugs[7,8]. Registry data from the United Kingdom and Sweden showed an increased risk of serious infection, especially in the first 6-12 months of therapy[2,9]. Most of the SI are caused by the same microorganisms commonly seen in the general population, but may also be due to opportunistic organisms that do not usually cause infections in an immunocompetent individual[2]. Some predictors of infection in RA include patient factors (older age, concomitant illness), disease-specific factors (level of disease activity and disability) and immunosuppression, especially with corticosteroid exposure, as cDMARDs appear to have little impact on infectious risk[9].

There is still controversy about the association between bDMARDs and SI, namely the magnitude of the risk and whether it varies among different subpopulations of patients with RA[10]. In fact, the mechanisms that lead to the increased risk of SI in bDMARDs are still not fully understood[8]. As bDMARDs act on different cellular and cytokine targets, it should be expected that there may be differences in the incidence and pattern of SI across bDMARD groups with different modes of action, but there are few studies directly comparing different bDMARDs[8,9].

As there are currently no national data on SI under different bDMARDs in Portuguese patients with RA, the main objectives of this study were to compare the incidence and site of SI in these patients and to determine possible predictors of SI in our population, hence becoming the first study to demonstrate national data on this topic.

MATERIALS AND METHODS

Study design: We performed an observational, multicenter retrospective cohort study including patients registered in the Rheumatic Diseases Portuguese Registry (Reuma.pt) with a diagnosis of RA performed by a Rheumatologist and exposed to at least one bDMARD until April 2021, from thirteen Portuguese Rheumatology centers. This study was carried out in accordance with the principles of the Declaration of Helsinki (revised in Fortaleza – 2013) and after approval by the Ethics Committee of Centro Hospitalar Universitário de São João and Reuma.pt.

Infections: Patients with at least one report of SI under bDMARD in Reuma.pt were compared to patients with no report of SI. SI was defined as an infection that motivated hospitalization, use of parenteral antibiotics or resulted in death. The site of infection was determined according to the ICD-10 classification (International Classification of Diseases 10th Revision) regarding organic systems (certain infectious and parasitic diseases, diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism, diseases of the nervous system, diseases of the eye and adnexa, diseases of the ear and mastoid process, diseases of the circulatory system, diseases of the respiratory system, diseases of the digestive system, diseases of the skin and subcutaneous tissue, diseases of the musculoskeletal system and connective tissue, diseases of the genitourinary system). Multiple SI in the same patient were included and examined, and data were collected for each event.

Data collection: We collected demographic and clinical data at baseline and at the time of each SI to establish comparisons between different groups of bDMARDs. For patients who never experienced a SI, we collected demographic and clinical data at baseline and at the last evaluation registered in Reuma.pt until April 2021. Variables collected at these timepoints were age, date of infection/last evaluation, gender, disease duration, disease activity – erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Disease Activity Score-28 using 4 variables (DAS284V-ESR and DAS284V-CRP), Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI) –, Health Assessment Questionnaire (HAQ), corticosteroid use and dosage (in equivalent dose of prednisolone), cDMARD, bDMARD, treatment duration of bDMARD, site of infection, mortality, and decision after infection (switch, discontinuation or maintenance of bDMARD, evaluated 6 months after SI), neoplasm history, previous orthopedic surgeries, other comorbidities (smoking, chronic obstructive pulmonary disease, asthma, interstitial lung disease), chronic kidney disease (at least stage 3) and diabetes mellitus.

Data analysis: Categorical variables are presented using absolute and relative frequencies; for continuous variables, mean, standard deviation, median and

interquartile range are shown, after assessment for normality using Shapiro-Wilk and histogram analysis. Comparisons between different bDMARDs were assessed using chi-square/Fisher's exact test, and Mann-Whitney U, Kruskal-Wallis, and t-test. Logistic regression was performed to identify predictors of SI among RA patients exposed to bDMARDs. Statistical analysis was performed using SPSS software (IBM, version 25). Two-sided P-values <0.050 were considered statistically significant.

RESULTS

Baseline: We included a total of 3394 patients, 2833 (83.5%) female, with a mean age at RA diagnosis of 45.5±13.7 years.

Four hundred and four (11.9%) had previous orthopedic surgeries and 388 patients were smokers (11.4%); regarding comorbidities, 293 patients (8.3%) had history of diabetes mellitus, 141 (4.2%) cancer, 129 (3.8%) interstitial lung disease (ILD), 58 (1.7%) chronic kidney disease (CKD), 54 (1.6%) asthma, and 23 (0.7%) chronic obstructive pulmonary disease (COPD). SI was diagnosed in 142 of the 3394 patients evaluated (4.2%). Clinical and demographics at the beginning of the first bDMARD are shown in Table I.

At baseline, comparing patients who were diagnosed with SI and patients without SI, there was a significantly higher proportion of patients with SI and previous orthopedic surgery (33.1% vs 11.0%, p<0.001), ILD (12.0% vs 3.4%, p<0.001), CKD (7.0% vs 1.5%, p<0.001), asthma (4.2% vs 1.5%, p=0.024), corticosteroid use (87.3% vs 77.1%, p=0.004), mean age at first bDMARD (57.2±12.5 vs 53.4±13.0 years, p=0.001) and median disease duration at first bDMARD – [10.3 (4.2-18.7) vs 7.4 (3.5-14.1) years, p=0.005] (Table II).

Severe Infections: As mentioned earlier, SI were identified in 142 patients, with some patients having more than one SI (n=9), totalizing 151 infections (4.4%). Among the identified SI, most were respiratory (n=63; 41.7%), the remainder being skin and subcutaneous tissue (n=31; 20.5%), genitourinary (n=22; 14.6%), musculoskeletal (n=15; 9.9%), gastrointestinal (n=10; 6.6%), circulatory and other infectious and parasitic diseases (each n=3; 2.0%), eyes and adnexa and nervous systems (each n=2; 1.3%). Nine patients died because of SI (6.0%). Of note, we found 11 cases of tuberculosis (7.3% of total SI), of which 9 were respiratory (pulmonary), 1 genitourinary (renal) and 1 gastrointestinal (hepatic). Those patients were all under anti-TNFα agents – adalimumab (n=6), infliximab (n=3) and etanercept (n=2). Ninety-two SI

Table I. Clinical and demographic data of the rheumatoid arthritis patients included in the study, at the beginning of the first bDMARD.

Variables	Total (n=3394)
Female gender – n (%)	2833 (83.5)
Age at diagnosis – mean (SD)	45.5 (13.7)
Previous orthopedic surgery – n (%)	404 (11.9)
Smoker – n (%)	388 (11.4)
Diabetes mellitus – n (%)	293 (8.6)
Lung disease – n (%) • Interstitial lung disease • Asthma • Chronic obstructive pulmonary disease	197 (5.8) 129 (3.8) 54 (1.6) 23 (0.7)
Past neoplasm – n (%)	141 (4.2)
Chronic kidney disease – n (%)	58 (1.7)
First bDMARD – n (%) • Etanercept • Adalimumab • Infliximab • Tocilizumab • Golimumab • Rituximab • Certolizumab • Anakinra • Abatacept • Secukinumab	 1309 (38.6) 679 (20.0) 439 (12.9) 348 (10.3) 297 (8.8) 189 (5.6) 94 (2.8) 26 (0.8) 12 (0.4) 1 (0.0)
Corticosteroid use – n (%) Corticosteroid dosage, mg – median (IQR)	2624 (77.3) 5 (2.5-7.5)
cDMARD – n (%) • Methotrexate • Hydroxychloroquine • Sulfasalazine • Leflunomide	2951 (86.9) 2486 (73.2) 665 (19.6) 632 (18.6) 563 (16.6)
Severe infection – n (%)	142 (4.2)
Age at first bDMARD – mean (SD) Disease duration at first bDMARD – median (IQR)	53.5 (13.0) 7.5 (3.5-14.3)
ESR, mm/1st h – median (IQR)	31 (17-51)
CRP, mg/L – median (IQR)	11.0 (4.1-23.4)
DAS284V-ESR – mean (SD)	5.4 (1.3)
DAS284V-CRP – mean (SD)	4.9 (1.2)
SDAI – mean (SD)	29.1 (13.7)
CDAI – mean (SD)	27.3 (12.9)
HAQ – mean (SD)	1.4 (0.7)

bDMARD – biological disease modifying anti-rheumatic drug; CDAI – Clinical Disease Activity Index; cDMARD – conventional disease modifying anti-rheumatic drug; CRP – C-reactive protein; DAS284V – Disease Activity Score-28 using 4 variables; ESR – Erythrocyte sedimentation rate; HAQ – Health Assessment Questionnaire; IQR – Interquartile range; SD – Standard deviation; SDAI – Simplified Disease Activity Index.

Table II. Comparison between patients with and without serious infection at baseline.

Variables	No infection (n=3252)	Infection (n=142)	p value
Female gender – n (%)	2713 (83.4)	120 (84.5)	0.734
Age at diagnosis – mean (SD)	45.4 (13.7)	46.7 (14.2)	0.290
Smoker – n (%)	369 (11.4)	19 (13.4)	0.515
Previous orthopedic surgery – n (%)	357 (11.0)	47 (33.1)	**<0.001**
Diabetes mellitus – n (%)	276 (8.5)	17 (12.0)	0.148
Lung disease – n (%) • Interstitial lung disease • Asthma • Chronic obstructive pulmonary disease	174 (5.4) 112 (3.4) 48 (1.5) 20 (0.6)	23 (16.2) 17 (12.0) 6 (4.2) 3 (2.1)	**<0.001** **<0.001** **0.024** 0.069
Past neoplasm – n (%)	132 (4.1)	9 (6.3)	0.183
Chronic kidney disease – n (%)	48 (1.5)	10 (7.0)	**<0.001**
Corticosteroid use – n (%)	2500 (77.1)	124 (87.3)	**0.004**
Age at first bDMARD – mean (SD) Disease duration at first bDMARD – median (IQR)	53.4 (13.0) 7.4 (3.5-14.1)	57.2 (12.5) 10.3 (4.2-18.7)	**0.001** **0.005**

bDMARD – biological disease modifying anti-rheumatic drug; IQR – Interquartile range; SD – Standard deviation.

(60.9%) occurred with the use of first line bDMARDs, with the majority of SI leading to discontinuation of the bDMARD at 6 months (n=75, 49.7%), while 65 (43.0%) restarted the same bDMARD and 11 (7.3%) switched to another bDMARD (6 to a different mode of action). The clinical and laboratory characteristics of SI are described in Table III. RA patients with SI were compared to those with no SI (Table IV). We found an association between SI and infliximab (12.6% vs 5.5%, p<0.001), rituximab (19.9% vs 11.8%, p=0.003), corticosteroid use (85.2% vs 58.9%, p<0.001), cDMARD (80.5% vs 73.2%, p=0.047), sulfasalazine use (16.1% vs 9.3%, p=0.006), ESR – [34 (13-49) vs 18 (8-34), p<0.001] –, CRP – [7.2 (2.2-16.0) vs 2.8 (1.0-8.0), p<0.001] –, DAS284V-ESR (4.1±1.5 vs 3.3±1.4, p<0.001), DAS284V-CRP (3.5±1.3 vs 2.8±1.3, p<0.001), HAQ (1.5±0.8 vs 1.1±0.5, p<0.001) and corticosteroid dose – [5 (5-7.5) vs 5 (0-5) mg/day, p<0.001]; on the other hand, the use of certolizumab (0% vs 3.4%, p=0.015) was negatively associated with SI.

Predictors of severe infections: We performed univariable logistic regression analysis and found that CKD – [Odds Ratio (OR) 5.76, confidence interval (CI) 95% 2.99-11.09; p<0.001] –, previous orthopedic surgery (OR 4.26, CI 95% 2.99-6.06; p<0.001), interstitial lung disease (OR 3.56, CI 95% 2.07-6.09; p<0.001), asthma (OR 2.76, CI 95% 1.16-6.56; p=0.021), corticosteroid use at baseline (OR 2.07, CI 95% 1.27-3.37; p=0.004), longer disease duration at the start of the first bDMARD (OR 1.03, CI 95% 1.01-1.04; p=0.001), older age at first bDMARD (OR 1.02, CI 95% 1.01-1.04; p=0.001) were baseline variables associated with SI; corticosteroid use (OR 4.04, CI 95% 2.55-6.38; p<0.001), higher HAQ (OR 2.23, CI 95% 1.77-2.81; p<0.001), rituximab (OR 2.10, CI 95% 1.22-3.56; p=0.007), infliximab (OR 2.02, CI 95% 1.36-3.00; p<0.001), sulfasalazine use (OR 1.88, CI 95% 1.19-2.96; p=0.006), higher DAS284V-ESR (OR 1.46, CI 95% 1.31-1.64; p<0.001), higher DAS284V-CRP (OR 1.45, CI 95% 1.29-1.63; p<0.001), higher corticosteroid dose (OR 1.09, CI 95% 1.06-1.125; p<0.001), higher ESR (OR 1.02, CI 95% 1.01-1.02; p<0.001) and higher CRP (OR 1.01, CI 95% 1.00-1.02; p<0.001) at the last visit before SI were predictors of SI. Despite being previously associated with SI, the use of cDMARD (OR 1.50, CI 95% 0.99-2.27; p=0.053) was not a predictor of SI.

After adjusting for corticosteroid use at the time of SI, baseline corticosteroid use was not an independent predictor of SI; DAS284V-ESR remained an independent predictor of SI when adjusted for ESR (OR 1.37, CI 95% 1.19-1.56; p<0.001) and the same was found with DAS284V-CRP when adjusted for CRP (OR 1.41, CI 95% 1.24-1.61; p<0.001).

We decided to perform multivariable logistic regression analysis including CKD, previous surgery, interstitial lung disease, asthma, use of corticosteroids, HAQ, rituximab, infliximab, sulfasalazine, DAS284V-ESR (as a marker of disease activity, chosen over DAS284V-CRP due to the higher OR in the univariable analysis), and corticosteroid dose, to identify independent predictors of SI. CKD, asthma, infliximab, corticosteroid use, interstitial lung disease, previous orthopedic surgery, HAQ and DAS284V-ESR were

Table III. Clinical and laboratory data of patients with severe infections.

Variables	Infection (n=151)
System – n (%)	
• Respiratory	63 (41.7)
• Skin and subcutaneous tissue	31 (20.5)
• Genitourinary	22 (14.6)
• Musculoskeletal	15 (9.9)
• Gastrointestinal	10 (6.6)
• Circulatory	3 (2.0)
• Other	3 (2.0)
• Eyes and adnexa	2 (1.3)
• Nervous	2 (1.3)
Death – n (%)	9 (6.0)
Previous infection – n (%)	9 (6.0)
bDMARD – n (%)	
• Etanercept	41 (27.2)
• Rituximab	30 (19.9)
• Tocilizumab	26 (17.2)
• Adalimumab	23 (15.2)
• Infliximab	19 (12.6)
• Golimumab	11 (7.3)
• Abatacept	1 (0.7)
First line bDMARD – n (%)	92 (60.9)
bDMARD decision – n (%)	
• Stop	75 (49.7)
• Restart	65 (43.0)
• Switch	11 (7.3)
Corticosteroid use – n (%)	127 (85.2)
CCT dosage, mg – median (IQR)	5 (5-7.5)
cDMARD – n (%)	120 (80.5)
• Methotrexate	96 (64.9)
• Sulfasalazine	24 (16.1)
• Leflunomide	20 (13.4)
• Hydroxychloroquine	18 (12.1)
Age – mean (SD)	61.8 (12.3)
Disease duration – median (IQR)	16.4 (8.7-24.3)
Duration of bDMARD – median (IQR)	1 (0-4)
ESR, mm/1st h – median (IQR)	34 (13-49)
CRP, mg/L – median (IQR)	7.2 (2.2-16.0)
DAS284V-ESR – mean (SD)	4.1 (1.5)
DAS284V-CRP – mean (SD)	3.5 (1.3)
SDAI – mean (SD)	17.0 (12.4)
CDAI – mean (SD)	15.7 (11.9)
HAQ – mean (SD)	1.5 (0.8)

bDMARD – biological disease modifying anti-rheumatic drug; CDAI – Clinical Disease Activity Index; cDMARD – conventional disease modifying anti-rheumatic drug; CRP – C-reactive protein; DAS284V – Disease Activity Score-28 using 4 variables; ESR – Erythrocyte sedimentation rate; HAQ – Health Assessment Questionnaire; IQR – Interquartile range; SD – Standard deviation; SDAI – Simplified Disease Activity Index.
Note: Laboratory and clinical evaluation of disease activity were collected at the last visit before diagnosis of severe infection.

all independent predictors of SI, while the remaining variables (rituximab, sulfasalazine, and corticosteroid dose) were not found to be independently associated with SI (Table V). Of note, previous orthopedic surgery was significantly associated both with musculoskeletal (including septic arthritis) and non-musculoskeletal SI.

First and second line bDMARD: We looked for differences between infections that occurred with the first bDMARD and with subsequent bDMARD (Table VI). We found an association between SI with subsequent bDMARDs and deaths (11.9% vs 2.2%, p=0.028), tocilizumab (28.8% vs 9.8%, p=0.003), rituximab (28.8% vs 14.1%, p=0.027), and an association between SI with first bDMARD and etanercept (35.9% vs 13.6%, p=0.003), infliximab (18.5% vs 3.4%, p= 0.006) and hydroxychloroquine (16.5% vs 5.2%, p=0.039), while we did not find statistically significant differences in relation to different sites of infection.

We also evaluated each bDMARD, looking for potential risk factors for SI within each bDMARD:

- Adalimumab – previous orthopedic surgery (34.8% vs 9.4%, p=0.001), CKD (17.4% vs 1.3%, p=0.001), previous SI (4.3% vs 0%, p=0.037), higher mean DAS284V-ESR (4.6±1.6 vs 3.4±1.3, p<0.001), DAS284V-CRP (3.9±1.5 vs 2.9±1.3, p=0.001), SDAI (19.2±13.4 vs 11.4±10.0, p=0.003), CDAI (17.9±12.2 vs 10.9±9.9, p=0.005), and higher median ESR ([36 (14-63) vs 19 (9-33) mm/1st h, p=0.011];
- Etanercept – previous orthopedic surgery (31.7% vs 9.8%, p<0.001), interstitial lung disease (12.2% vs 2.0%, p=0.002), CKD (9.8% vs 1.3%, p=0.004), previous SI (7.3% vs 0%, p<0.001), use of corticosteroid (82.9% vs 55.1%, p<0.001); older age (64.4±9.7 vs 59.7±13.1 years, p=0.022), DAS284V-ESR (4.0±1.4 vs 3.3±1.3, p=0.002), DAS284V-CRP (3.3±1.4 vs 2.7±1.3, p=0.010), SDAI (15.4±11.7 vs 10.2±10.2, p=0.006), CDAI (13.9±10.7 vs 9.4±9.5, p=0.010), HAQ (1.3±1.0 vs 0.9±0.8, p=0.016); higher median ESR [36 (17-55) vs 19 (9-33) mm/1st h, p=0.003], CRP [7.5 (2.9-22.2) vs 3 (1.2-7.9) mg/L, p=0.002], and corticosteroid dose – 5 (5-7.5) vs 2.5 (0-5) mg, p<0.001;
- Golimumab – previous SI (9.1% vs 0%, p=0.043); higher mean DAS284V-ESR (4.5±1.6 vs 3.1±1.2, p<0.001), DAS284V-CRP (3.7±1.6 vs 2.5±1.1, p=0.001), and HAQ (1.8±0.7 vs 0.9±0.7, p<0.001);
- Infliximab – previous orthopedic surgery (47.4% vs 16.2%, p=0.003), corticosteroid use (94.7% vs 56.5%, p=0.001) and methotrexate use (100% vs 71.6%, p=0.004); higher mean DAS284V-ESR (4.5±1.0 vs 3.7±1.3, p=0.004), DAS284V-CRP (3.8±1.1 vs 2.9±1.3, p=0.009), SDAI (20.1±10.7 vs 11.3±10.2, p=0.001), CDAI (17.9±10.8 vs 10.3±9.7, p=0.003), HAQ (1.6±0.7 vs 1.2±0.8, p=0.043), and higher median corticosteroid dose [5 (5-7.5) vs 5 (0-5) mg, p=0.002];

Table IV. Comparison between rheumatoid arthritis patients with severe infections versus those with no infections at the last visit before severe infection versus last recorded visit, respectively.

Variables	No severe infection (n=3252)	Severe infection (n=151)	p value
bDMARD – n (%)			
Etanercept	1049 (32.3)	41 (27.2)	0.189
Tocilizumab	625 (19.2)	26 (17.2)	0.541
Adalimumab	596 (18.3)	23 (15.2)	0.335
Rituximab	384 (11.8)	30 (19.9)	**0.003**
Golimumab	244 (7.5)	11 (7.3)	0.921
Infliximab	179 (5.5)	19 (12.6)	**<0.001**
Certolizumab	109 (3.4)	0 (0)	**0.015**
Abatacept	53 (1.6)	1 (0.7)	0.516
Anakinra	10 (0.3)	0 (0)	0.635
Ustekinumab	1 (0.0)	0 (0)	0.956
First line bDMARD – n (%)	2145 (66.0)	92 (60.9)	0.203
Corticosteroid use – n (%)	1812 (58.9)	127 (85.2)	**<0.001**
CCT dosage, mg – median (IQR)	5 (0-5)	5 (5-7.5)	**<0.001**
cDMARD – n (%)	2252 (73.2)	120 (80.5)	**0.047**
Methotrexate	1816 (59.0)	96 (64.9)	0.157
Leflunomide	366 (11.9)	20 (13.4)	0.575
Hydroxychloroquine	339 (10.4)	18 (12.1)	0.686
Sulfasalazine	285 (9.3)	24 (16.1)	**0.006**
Combination	456 (20.2)	32 (26.4)	0.097
Age – mean (SD)	59.9 (12.8)	61.8 (12.3)	0.069
ESR, mm/1st h – median (IQR)	18 (8-34)	34 (13-49)	**<0.001**
CRP, mg/L – median (IQR)	2.8 (1.0-8.0)	7.2 (2.2-16.0)	**<0.001**
DAS284V-ESR – mean (SD)	3.3 (1.4)	4.1 (1.5)	**<0.001**
DAS284V-CRP – mean (SD)	2.8 (1.3)	3.5 (1.3)	**<0.001**
SDAI – mean (SD)	11.1 (10.4)	17.0 (12.4)	**<0.001**
CDAI – mean (SD)	10.3 (9.9)	15.7 (11.9)	**<0.001**
HAQ – mean (SD)	1.1 (0.8)	1.5 (0.8)	**<0.001**

bDMARD – biological disease modifying anti-rheumatic drug; CDAI – Clinical Disease Activity Index; cDMARD – conventional disease modifying anti-rheumatic drug; CRP – C-reactive protein; DAS284V – Disease Activity Score-28 using 4 variables; ESR – Erythrocyte sedimentation rate; HAQ – Health Assessment Questionnaire; IQR – Interquartile range; SD – Standard deviation; SDAI – Simplified Disease Activity Index.

Table V. Multivariable logistic regression analysis for occurrence of severe infections among RA patients under bDMARDs.

	Odds ratio	95% Confidence Interval	p value
Chronic kidney disease	4.67	2.100-10.397	<0.001
Asthma	3.29	1.233-8.807	0.017
Infliximab	2.86	1.564-5.210	0.001
Corticosteroid use	2.84	1.492-5.394	0.001
Interstitial lung disease	2.70	1.386-5.248	0.003
Previous orthopedic surgery	2.61	1.702-3.999	<0.001
Corticosteroid dose	1.43	0.910-1.037	0.388
Health Assessment Questionnaire	1.41	1.065-1.864	0.016
DAS284V-ESR	1.26	1.097-1.456	0.001
Rituximab	1.05	0.622-1.784	0.847
Sulfasalazine	0.85	0.845-2.415	0.183

DAS284V-ESR – Disease Assessment Score-28 using 4 variables with erythrocyte sedimentation rate.

Table VI. Comparison between severe infections with the first bDMARD and subsequent bDMARDs.

Variables	First bDMARD (n=92)	Second line (n=59)	p value
System – n (%)			
Respiratory	35 (38.0)	28 (47.4)	0.252
Skin and subcutaneous tissue	18 (19.6)	13 (22.0)	0.714
Genitourinary	17 (18.5)	5 (8.5)	0.089
Musculoskeletal	9 (9.8)	6 (10.2)	0.938
Gastrointestinal	4 (4.3)	6 (10.2)	0.190
Circulatory	2 (2.2)	1 (1.7)	0.662
Eyes and adnexa	2 (2.2)	0 (0)	0.521
Nervous	2 (2.2)	0 (0)	0.521
Other	3 (3.3)	0 (0)	0.281
Death – n (%)	2 (2.2)	7 (11.9)	**0.028**
bDMARD – n (%)			
Etanercept	33 (35.9)	8 (13.6)	**0.003**
Infliximab	17 (18.5)	2 (3.4)	**0.006**
Rituximab	13 (14.1)	17 (28.8)	**0.027**
Adalimumab	12 (13.0)	11 (18.6)	0.350
Tocilizumab	9 (9.8)	17 (28.8)	**0.003**
Golimumab	8 (8.7)	3 (5.1)	0.529
Abatacept	0 (0)	1 (1.7)	0.391
bDMARD decision – n (%)			
Stop	40 (43.5)	35 (59.3)	0.057
Restart	44 (47.8)	21 (35.6)	0.139
Switch	8 (8.7)	3 (5.1)	0.529
Corticosteroid – n (%)	79 (86.8)	48 (82.8)	0.496
cDMARD – n (%)	76 (83.5)	44 (75.9)	0.250
Methotrexate	59 (64.8)	37 (64.9)	0.992
Sulfasalazine	17 (18.7)	7 (12.1)	0.284
Leflunomide	14 (15.4)	6 (10.2)	0.379
Hydroxychloroquine	15 (16.5)	3 (5.2)	**0.039**

bDMARD – biological disease modifying anti-rheumatic drug; cDMARD – conventional disease modifying anti-rheumatic drug.

- Rituximab – COPD (6.7% vs 0.5%, p=0.028), higher mean HAQ (1.8±0.6 vs 1.4±0.8, p=0.009), higher median CRP [10.9 (5.7-19.6) vs 5.2 (2-12.4) mg/L, p=0.008], and PDN dose [5 (5-7.5) vs 5 (0-5) mg, p=0.044];
- Tocilizumab – previous orthopedic surgery (38.5% vs 10.6%, p<0.001), past neoplasm (15.4% vs 1.6%, p=0.002), CKD (11.5% vs 1.9%, p=0.019), corticosteroid use (92.3% vs 59.8%, p=0.001), cDMARD (88.5% vs 61.3%, p=0.005); higher mean DAS284V-ESR (3.8±1.9 vs 2.9±1.5, p=0.002), DAS284V-CRP (3.4±1.5 vs 2.7±1.3, p=0.011), SDAI (17.4±13.2 vs 11.3±10.7, p=0.007), CDAI (16.8±13.1 vs 10.9±10.1, p=0.039), HAQ (1.5±0.7 vs 1.1±0.7, p=0.007); higher median ESR [16 (5-39) vs 7 (4-16) mm/1st h, p=0.036], CRP [2.4 (0.8-10.2) vs 0.7 (0.3-2.7) mg/L, p=0.003], and corticosteroid dose [5 (5-7.5) vs 5 (0-5) mg, p<0.001].

Comparisons between different single versus multiple SI: We did not find any statistically significant differences between patients with single and multiple (n=9) SI, both at baseline and at the time of SI (data not shown).

DISCUSSION

This comprehensive study included 3394 patients, with a total of 4.2% of SI in this sample. The rate of SI in this cohort of Portuguese patients with RA is similar to that reported in other studies[9,11-13]. At baseline, RA patients with SI had significantly higher rates of prior orthopedic surgery, lung disease (asthma and interstitial lung disease), CKD, corticosteroid use at baseline, older age and longer duration of illness. A multicenter study in the United States, including 10484 RA patients under anti-TNFα agents, also reported that baseline glucocorticoid was significantly associated with increased hospitalization risk compared with no baseline use, with the risk being greater with higher doses[14]. Other factors, such as diabetes mellitus and COPD, have been described in recent studies, such as one from the British Society of Rheumatology registry[4,14], but were not associated with SI in this Portuguese study.

Most patients had respiratory infections, but skin and subcutaneous tissue and genitourinary infections

together represented more than 75% of the observed SI. This is in agreement with other studies, which report pneumonia as the most common SI complication, contributing to 42-53% of the SI[9,14]. Mortality rate was 6.0% in this Portuguese sample. A former study looking at mortality found that over 10% of patients with a SI died within 30 days, with sepsis being a significant predictor of mortality[9].

The majority of patients had SI with their first prescribed bDMARD (60.9%), and almost half (49.7%) had no bDMARD prescribed 6 months after SI (43.0% restarted the same bDMARD and 7.3% switched to another bDMARD). This means that SI are a critical factor in the treatment options for the Portuguese RA patient, as more than half will not be on the same bDMARD 6 months after the SI. A study looking at bDMARD decision after SI with anti-TNFα found that almost 80% restarted the same anti-TNF medication, while 5% switched to another bDMARD and 16% did not receive any biologic medication for 18 months[8].

We found associations between SI and infliximab, rituximab, corticosteroid, cDMARD, sulfasalazine, ESR, CRP, disease activity by DAS284V, HAQ, and corticosteroid dose, while no certolizumab users had SI, which was a statistically significant difference. Although a previous Cochrane review from 2011 found higher rates of infection with certolizumab when compared with other anti-TNF drugs, this was not confirmed in more recent studies, and certolizumab is regarded as a somewhat safer bDMARD in people with higher infectious risk[9,15], similar to what was found in this study.

In multivariable models, chronic kidney disease, asthma, infliximab, corticosteroid use, interstitial lung disease, previous orthopedic surgery, HAQ and DAS284V-ESR were independent predictors of SI, while rituximab, cDMARD, sulfasalazine and corticosteroid dose were not, which it likely means that other factors are responsible for increasing risk of SI with the latter. The 2011 Cochrane review also identified patients who received cDMARD as having a more pronounced risk of SI[15]. There are still controversial data on comparisons between bDMARDs[3]. A systematic literature review highlighted eight studies that did not show differences between several drugs, although one found a signal of increased risk of SI with infliximab compared with etanercept and another for infliximab, etanercept and rituximab compared with abatacept[3,16-23]. Another study found infliximab to be the anti-TNFα drug most associated with SI, especially when compared with etanercept and adalimumab[14]. With respect to rituximab, a study comparing bDMARDs found higher rates of SI in rituximab compared with anti-TNFα drugs[24], but likely, in our study, the higher incidence of infections may be due to higher rates of interstitial lung disease in patients receiving rituximab, and not an effect of the drug *per se*. The same was found in a previous study, where, in the unadjusted analysis, rituximab had a higher incidence of infection than etanercept, but in the adjusted analysis, the difference was no longer statistically significant[9]. The authors hypothesize that the difference may be due to patients with rituximab receiving it as a second line bDMARD[9]. This is in agreement with previous studies that showed similar infectious risk with rituximab and anti-TNFα drugs and even placebo[4].

We also looked at differences between SI that occurred with first and subsequent bDMARD. Most infections with tocilizumab and rituximab occurred with their use as second line bDMARD, which coincides with how these drugs are usually employed in RA. We also found an interesting association with SI leading to death in patients in whom the associated bDMARD was a second line bDMARD.

The main strengths of this study are the use of real-world data from a large sample of biologic-treated patients with a long follow-up period, using the national database Reuma.pt. We performed a comprehensive analysis, which included data from previous medical history/comorbidities that are known to enhance infectious risk, concomitant medication, and clinical and laboratory measures of disease activity. The main limitations of this study are those derived from its observational nature, since the patients were not randomized, and the data are more exposed to selection bias. We tried to adjust the results to several clinical data, but there are potential confounders for which we could not adjust. Another limitation of the study is the lack of information regarding the agents that caused SI and other outcomes of SI besides death (and, in those cases, the cause of death) and change/maintenance of immunomodulatory therapy.

In conclusion, this study described the incidence and types of SI among RA patients under biologics in our Portuguese national registry, identified several predictors of SI in this population and highlighted differences between different bDMARDs in a large cohort. bDMARDs are an effective and safe option for treating RA, but the risk of infection is present, and clinicians should be aware of that real-world risk when making treatment decisions between different bDMARDs.

REFERENCES

1. Singh JA, Saag KG, Bridges SL et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Rheumatol. 2016;68(1):1-26.
2. Rutherford AI, Patarata E, Subesinghe S, Hyrich KL, Galloway JB. Opportunistic infections in rheumatoid arthritis patients

exposed to biologic therapy: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. Rheumatology (Oxford). 2018;57(6):997-1001.
3. Ramiro S, Sepriano A, Chatzidionysiou K, et al. Safety of synthetic and biological DMARDs: a systematic literature review informing the 2016 update of the EULAR recommendations for management of rheumatoid arthritis. Ann Rheum Dis. 2017;76(6):1101-1136.
4. Holroyd CR, Seth R, Bukhari M, et al. The British Society for Rheumatology biologic DMARD safety guidelines in inflammatory arthritis. Rheumatology (Oxford). 2019;58(2):e3-e42.
5. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. Arthritis Rheum. 2002;46(9):2287-2293.
6. Cohen S, Radominski SC, Gomez-Reino JJ et al. Analysis of infections and all-cause mortality in phase II, phase III, and long-term extension studies of tofacitinib in patients with rheumatoid arthritis. Arthritis Rheumatol. 2014;66(11):2924-2937.
7. Minozzi S, Bonovas S, Lytras T et al. Risk of infections using anti-TNF agents in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: a systematic review and meta-analysis. Expert Opin Drug Saf. 2016;15(sup1):11-34.
8. 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(6):1065-1071.
9. 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(6):905-910.
10. 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(9990):258-265.
11. Askling J, Fored CM, Brandt L et al. Time-dependent increase in risk of hospitalisation with infection among Swedish RA patients treated with TNF antagonists. Ann Rheum Dis. 2007;66(10):1339-1344.
12. Singh JA, Christensen R, Wells GA et al. Biologics for rheumatoid arthritis: an overview of Cochrane reviews. Cochrane Database of Systematic Reviews. 2009(4).
13. Winthrop KL. Infections and biologic therapy in rheumatoid arthritis: our changing understanding of risk and prevention. Rheum Dis Clin North Am. 2012;38(4):727-745.
14. Grijalva CG, Chen L, Delzell E et al. Initiation of tumor necrosis factor-alpha antagonists and the risk of hospitalization for infection in patients with autoimmune diseases. Jama. 2011;306(21):2331-2339.
15. Singh JA, Wells GA, Christensen R et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview. Cochrane Database of Systematic Reviews. 2011(2).
16. Aaltonen KJ, Joensuu JT, Virkki L et al. Rates of serious infections and malignancies among patients with rheumatoid arthritis receiving either tumor necrosis factor inhibitor or rituximab therapy. J Rheumatol. 2015;42(3):372-378.
17. Chiu YM, Lang HC, Lin HY et al. Risk of tuberculosis, serious infection and lymphoma with disease-modifying biologic drugs in rheumatoid arthritis patients in Taiwan. Int J Rheum Dis. 2014;17 Suppl 3:9-19.
18. Lampropoulos CE, Orfanos P, Bournia VK, et al. Adverse events and infections in patients with rheumatoid arthritis treated with conventional drugs or biologic agents: a real world study. Clin Exp Rheumatol. 2015;33(2):216-224.
19. Chiang YC, Kuo LN, Yen YH, Tang CH, Chen HY. Infection risk in patients with rheumatoid arthritis treated with etanercept or adalimumab. Comput Methods Programs Biomed. 2014;116(3):319-327.
20. Curtis JR, Yang S, Patkar NM et al. Risk of hospitalized bacterial infections associated with biologic treatment among US veterans with rheumatoid arthritis. Arthritis Care Res (Hoboken). 2014;66(7):990-997.
21. Johnston SS, Turpcu A, Shi N, Fowler R, Chu BC, Alexander K. Risk of infections in rheumatoid arthritis patients switching from anti-TNF agents to rituximab, abatacept, or another anti-TNF agent, a retrospective administrative claims analysis. Semin Arthritis Rheum. 2013;43(1):39-47.
22. Sakai R, Cho SK, Nanki T et al. Head-to-head comparison of the safety of tocilizumab and tumor necrosis factor inhibitors in rheumatoid arthritis patients (RA) in clinical practice: results from the registry of Japanese RA patients on biologics for long-term safety (REAL) registry. Arthritis Res Ther. 2015;17(1):74.
23. Yun H, Xie F, Delzell E et al. Comparative Risk of Hospitalized Infection Associated With Biologic Agents in Rheumatoid Arthritis Patients Enrolled in Medicare. Arthritis Rheumatol. 2016;68(1):56-66.
24. Cobo-Ibáñez T, Descalzo M, Loza-Santamaría E, Carmona L, Muñoz-Fernández S. Serious infections in patients with rheumatoid arthritis and other immune-mediated connective tissue diseases exposed to anti-TNF or rituximab: data from the Spanish registry BIOBADASER 2.0. Rheumatol Int. 2014;34(7):953-961.
25. Berman M, Ben-Ami R, Berliner S et al. The Effect of Tocilizumab on Inflammatory Markers in Patients Hospitalized with Serious Infections. Case Series and Review of Literature. Life (Basel). 2021;11(3).