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# Incidence of Infectious Adverse Events in Patients With Rheumatoid Arthritis and Spondyloarthritis on Biologic Drugs—Data From the Brazilian Registry for Biologics Monitoring

*Mariana Cecconi, MD,* Roberto Ranza, MD,* David C. Titton, MD,† Júlio C. B. Moraes, MD,‡ Manoel Bertolo, MD,§ Washington Bianchi, MD,|| Claiton Brenol, MD,¶ Hellen M. Carvalho, MD,# Glaucio R. W. de Castro, MD,** Izaias P. Costa, MD,†† Maria F. L. Cunha, MD,‡‡ Ângela Duarte, MD,§§ Vander Fernandes, MD,|||| Marlene Freire, MD,¶¶ Paulo Louzada-Junior, MD,## José C. Macieira, MD,*** José R.S. Miranda, MD,††† Ivanio A. Pereira, MD,‡‡‡ Geraldo R.C. Pinheiro, MD,§§§ Barbara Stadler, MD,|||||| Roberto A. Toledo, MD,¶¶¶ Valeria Valim, MD,### Miguel A. Descalzo, PhD,**** Rogerio M.C. Pinto, PhD,†††† and Ieda Laurindo, MD‡‡‡‡*

**Background:** The safety profile of biologic drugs might present substantial regional differences. Since 2009, the Brazilian Society of Rheumatology has maintained BIOBADABRASIL (Brazilian Registry for Biologic Drugs), a registry for monitoring of biologic therapies in rheumatic diseases.

**Objectives:** The aim of this study was to verify the incidence rate (IR) of serious infections in rheumatoid arthritis (RA) and spondyloarthritis (SpA) patients on biologic drugs.

**Methods:** BIOBADABRASIL prospectively included patients with rheumatic diseases who started the first biologic drug or a synthetic disease-modifying antirheumatic drug as a parallel control group. This study focuses on serious infectious adverse events (SIAEs) in RA and SpA patients on biologic drugs compared with controls, from January 2009 to June 2015. Time of exposure was set from initiation of the drug to the date of last administration or censorship. Serious infectious adverse events IR was calculated per 1000 patient/years with 95% confidence interval (CI).

**Results:** A total of 1698 patients (RA, 1121; SpA, 577) were included, 7119 patient/years. Serious infectious adverse events were more common among patients on tumor necrosis factor inhibitors (TNFi's) than controls (adjusted IR ratio, 2.96 [95% CI, 2.01–4.36]; $p < 0.001$). Subsequent TNFi was associated with a higher SIAEs incidence when compared with first TNFI (adjusted IR ratio, 1.55 [95% CI, 1.15–2.08]; $p = 0.004$). Serious infectious adverse events were associated with age and corticosteroids intake. Serious infectious adverse events were more frequent in the respiratory tract in all subgroups.

**Conclusions:** In BIOBADABRASIL, biologic drugs, especially the subsequent TNFi, were associated with a higher risk of serious infections compared with synthetic DMARDs. Corticosteroid intake and age represented risk factors for SIAEs. Constant monitoring is required to follow the safety profile of drugs in the clinical setting of rheumatic conditions in Brazil.

**Key Words:** biological products, adverse drug events, rheumatoid arthritis, spondyloarthritis, registries

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Registries are an established method for monitoring the long-term safety of new approved antirheumatic drugs.[1] Pivotal studies demonstrate the effectiveness and safety of drugs during a set observation period in selected groups of patients. As a complementary approach, registries allow limitless observation of relevant pathologic events in individuals on treatment with new drugs, without restriction in the number of medications or comorbidities. In fact, registries are determinant in defining the real safety profile of medications in actual clinical situations. Because of the great regional variability in the epidemiology of diseases, especially infectious ones, local registries are extremely important to detect risk of specific adverse events in particular populations. The relationship between tumor necrosis factor inhibitors (TNFi's) biologics and risk of tuberculosis was first established by a registry study in a country with a relatively high incidence of the disease.[2] Furthermore, the effectiveness of a patient screening strategy to reduce that specific risk was confirmed by the same registry.[3] In 2009, the Brazilian Society of Rheumatology (BSR) implemented its own registry for active monitoring of biologic disease-modifying antirheumatic drugs (bDMARDs) in rheumatic diseases.[4] The strong points of this initiative were as follows: (1) since the beginning, it has been an institutional project, with the BSR as sponsor and owner of the data, ensuring scientific independence; (2) a solid methodology, with defined protocol and procedures manual[5]; (3) a 3-level data quality control[5]; (4) a platform in common with the established Spanish registry BIOBADASER,

From the *Universidade Federal de Uberlândia, Uberlândia; †Universidade Federal do Paraná, Curitiba; ‡Faculdade de Medicina, Universidade de São Paulo, São Paulo; §Universidade Estadual de Campinas, Campinas; ||Santa Casa Misericordia do Rio de Janeiro, Rio de Janeiro; ¶Universidade Federal do Rio Grande do Sul/Hospital de Clínicas de Porto Alegre, Porto Alegre; #Hospital Base do Distrito Federal, Brasilia; **Hospital Celso Ramos de Florianópolis, Florianópolis; ††HUMAP/EBSERH/UFMS, Campo Grande; ‡‡Universidade Federal do Pará, Belém; §§Universidade Federal de Pernambuco, Recife; ||||Hospital Geral Universitário de Cuiabá; ¶¶Universidade Federal do Triângulo Mineiro, Uberaba; ##USP Ribeirão Preto, Ribeirão Preto; ***Universidade Federal de Sergipe, Aracajú; †††Artrocenter Clínica Médica de Taubaté, Taubaté; ‡‡‡Universidade Federal de Santa Catarina, Florianópolis; §§§Universidade Estadual do Rio de Janeiro, Rio de Janeiro; ||||||Hospital Universitário Evangélico de Curitiba, Curitiba; ¶¶¶Faculdade de Medicina de São José do Rio Preto, São José do Rio Preto; ###Universidade Federal do Espírito Santo, Vitória; ****Research Unit, Academia Española de Dermatologia y Venereologia, Madrid; and ††††Faculdade de Matemática da Universidade Federal de Uberlândia, Uberlândia; and ‡‡‡‡Faculdade de Medicina da Universidade Nove de Julho, São Paulo, Brazil.

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Correspondence: Roberto Ranza, MD, Universidade Federal de Uberlandia–Campus Umuarama Uberlandia, Rua Otavio Rodrigues da Cunha, 548, 38411-176, Uberlandia, Minas Gerais, Brazil.
E-mail: robertoranza@gmail.com.



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which was also available for all other Latin America countries (BIOBADAMERICA project)[6]; and (5) through the BSR, the project was opened to all Brazilian rheumatology units to achieve national representability, including patients from all the country's states. Both controlled and registry studies pointed out that infectious adverse events are the most frequent in patients exposed to bDMARDs.[7,8] This study aimed to define the incidence of serious infectious adverse events (SIAEs) in patients with rheumatoid arthritis (RA) and spondyloarthritis (SpA) monitored in the Brazilian Registry for Biologic Drugs (BIOBADABRASIL).

## MATERIAL AND METHODS

BIOBADABRASIL is an observational, prospective, multicenter project with no time limitation. Patients have been included by 32 rheumatology units from almost all Brazilian states. A 3-domain online platform was used for data entry: (1) demographics, disease characteristics, comorbidities, and infectious diseases screening; (2) treatment; and (3) adverse events, with outcome information. Disease diagnosis, drug indication, and inclusion in the registry were decisions of the principal investigator of each center, but always according to predetermined guidelines. Patients could be included if they met the following criteria: (1) diagnosis of any rheumatic disease initiating the first bDMARD within the previous 3 months; (2) RA or SpA diagnosis starting a new synthetic disease-modifying antirheumatic drug (sDMARD), up to 3 months, with no previous exposure to bDMARDs (internal control group); and (3) signed informed consent. After inclusion, patients were on continuous follow-up. Data were compulsorily updated in case of an adverse event or treatment modification, registering the cause and the relationship with the drug in use. Adverse events were classified according to the Medical Dictionary for Regulatory Activities (MedDRA).[9] Definitions of severity and outcome of adverse events were stated in the BIOBADABRASIL protocol.[5] A serious adverse event (SAE) required notification and was defined as a condition that causes death or is life-threatening, implies inpatient hospitalization or prolongation of an existing one, and involves persistent or significant incapacity disability or a congenital abnormality/birth defect. Pregnancy was included among SAEs. Serious infectious adverse events were considered all SAEs with clinical characteristics of infection, ideally with the identification of the causative agent. Outcome of adverse events was categorized as follows: unknown, recovered with sequelae, recovered without sequelae, not recovered, death related to the event, death possibly related to the drug in use, and death with no relationship to the drug. Serious adverse events were assigned to a drug if they occurred during drug therapy or within a 90-day period after the last dose. If an event could be associated with several drugs, it was associated with all of them according to international recommendations.[1] A specifically trained monitor of the BSR maintained a constant 3-level data quality control program: (1) digital, using the platform resources; (2) by phone, contacting patients every 6 months; and (3) in loco, yearly, comparing registry data and medical files of 20% of patients randomly selected in each center. The local ethical committee of each center approved the study, and all patients signed the informed consent. BIOBADABRASIL is sponsored by the BSR, with funds from the different pharmaceutical companies marketing biological compounds in Brazil. In this study, we limited the analysis to patients with diagnosis of RA or SpA (ankylosing spondylitis and psoriatic arthritis) collected from January 2009 to June 2015. For a general perspective of bDMARDs SIAEs in our population, data of patients with RA and SpA were analyzed jointly and compared with the control group. To compare SIAE incidence in RA and SpA, we focused only on TNFi bDMARDs, because, until 2015, only adalimumab, etanercept, and infliximab were provided for SpA in our country. Subsequent TNFi was defined as the second or further biologic of this class used by the same patient. Afterward, RA data were analyzed independently to obtain a more consistent comparison of SIAE incidence between the bDMARDs and sDMARDs groups, because 92% of the latter is composed of RA patients, mainly on methotrexate and/or leflunomide. In RA, the non-TNFi's (abatacept, rituximab, tocilizumab) were analyzed as a group, due to their relatively small numbers.

### Statistical Methods

Time of exposure was set from initiation of the drug to the date of last administration plus twice the half-life or censorship. If there was overlap of multiple treatments for 1 patient, then a lag-window of 3 months was accounted for each biologic treatment.

Continuous variables were expressed as mean (SD), and categorical variables were expressed in absolute and percentage values. Student $t$ and $\chi^2$ tests were used to compare variables between groups with and without serious infections. The SIAE incidence rate (IR) was calculated per 1000 patient/years with 95% confidence interval (CI) and IR ratio (IRR) estimated between groups. The significance level was set at 0.05. The Poisson regression multivariable model was used to estimate adjusted IRR using age, sex, disease duration, corticosteroids, diabetes, and smoking status as confounding factors.

## RESULTS

The general characteristics of patients in the BIOBADABRASIL registry, as of June 2015, are presented in Table 1. The total included 1698 subjects with RA (1121, 66%) and SpA (577,

**TABLE 1.** BIOBADABRASIL Registry as of June 2015–General View

| | All Biologics | Synthetic DMARDs Controls | Total |
|---|---|---|---|
| No. patients | 2024 | 583 | 2607 |
| No. treatments (patient/years) | 2945 (8354) | 600 (2132) | 3545 (10486) |
| Female gender (%) | 1329 (67) | 481 (83) | 1810 (69) |
| Age at baseline, mean (SD), y | 45 (14.4) | 49.7 (12.8) | 46.1 (14.2) |
| Age at June 30, 2015, mean (SD), y | 49.6 (14.5) | 54.2 (13) | 50.7 (14.3) |
| RA (%) | 1121 (55) | 528 (91) | 1649 (63) |
| Ankylosing spondylitis (%) | 408 (20) | 36 (6) | 444 (17) |
| Psoriatic arthritis (%) | 169 (8) | 8 (1) | 177 (7) |
| Disease duration at baseline, mean (SD), y | 8.8 (7.9) | 5.5 (7.4) | 8.2 (7.9) |

**TABLE 2.** TNFi vs Synthetic DMARDs—Comparison of General Characteristics

| | TNFi RA and SpA | Synthetic DMARDs RA and SpA | TNFi RA | Synthetic DMARDs RA |
|---|---|---|---|---|
| Patients | 1601 | 572 | 1024 | 528 |
| Female gender (%) | 1039 (65) | 474 (83) | 868 (85) | 454 (86) |
| Age, mean (SD), y | 51.9 (12.5) | 54.6 (12.6) | 54.9 (11.8) | 54.8 (12.7) |
| Disease duration, mean (SD), y | 8.6 (7.9) | 5.3 (7.3) | 9.3 (8) | 5.4 (7.3) |
| Follow-up time, mean (SD), y | 2.9 (2.3) | 3.6 (2.2) | 2.8 (2.4) | 3.6 (2.2) |
| DAS, mean (SD) | — | — | 5.3 (1.3) | 5.1 (3.1) |
| Glucocorticoids use at baseline (%) | 929 (58) | 435 (76) | 791 (77) | 422 (80) |
| Methotrexate and/or leflunomide use at baseline (%) | 1153 (72) | 526 (92) | 910 (89) | 508 (96) |
| Diabetes (%) | 145 (9) | 52 (9) | 108 (11) | 52 (10) |
| Smokers (%) | 206 (13) | 86 (15) | 136 (13) | 78 (15) |
| Etanercept (%) | 396 (25) | — | 258 (25) | — |
| Infliximab (%) | 613 (38) | — | 363 (35) | — |
| Adalimumab (%) | 563 (35) | — | 375 (37) | — |
| Golimumab (%) | 20 (1) | — | 19 (1.9) | — |
| Certolizumab (%) | 9 (0.6) | — | 9 (0.9) | — |

34%) on biologic drugs, with 7119 patient/years and follow-up time of 2.8 (SD 2.2) years. Controls were 572 (RA, 528 [92%]; SpA, 44 [8%]), with 2093 patient/years and follow-up time of 3.6 (SD 2.2). In the biologic group, 1601 (94%) received a TNFi and 97 (6%) a non-TNFi as the first biologic. Controls were mainly on methotrexate (85%), leflunomide (40%), or both drugs (35%). Data comparing characteristics of RA and SpA patients on TNFi to the control group are shown in Table 2. Patients on sDMARDs had, in general, a shorter disease duration. In RA, the mean Disease Activity Score (DAS28) was similar in bDMARDs and controls while 11% on TNFi had no background sDMARD at baseline.

The overall IR of SIAEs for bDMARDs was 36 per 1000 patient/years (95% CI, 31–40; 253 infections) and for TNFi was 35 per 1000 patient/years (95% CI, 30–40; 218 infections) versus 15 per 1000 patient/years (95% CI, 10–21; 31 infections) for controls (IRR, 2.4 [95% CI, 1.65–3.49]; $p < 0.001$; IRR, 2.34 [95% CI, 1.6–3.5]; $p < 0.001$, respectively; adjusted IRR, 2.85 [95% CI, 1.94–4.17]; $p < 0.001$, and adjusted IRR, 2.96 [95% CI, 2.01–4.36]; $p < 0.001$, respectively). The IR on TNFi was higher in RA, 43 per 1000 patient/years (95% CI, 37–50), than in SpA 21 per 1000 patient/years (95% CI, 16–28; IRR, 0.5 [95% CI, 0.36–0.69]; $p < 0.001$), but statistical differences disappear after adjusted IRR of 0.96 (95% CI, 0.64–1.44; $p = 0.837$). An increased SIAE frequency was found when the subsequent TNFi treatment was compared with the first, 31 per 1000 patient/years (95% CI, 26–36) versus 50 per 1000 patient/years (95% CI, 39–64; IRR, 1.6 [95% CI, 1.17–2.17]; $p = 0.0013$, and adjusted IRR, 1.55 [95% CI, 1.15–2.08]; $p = 0.004$). There were limited >statistically significant differences in SIAEs between the most prescribed TNFi: adalimumab versus infliximab (adjusted IRR, 0.71 [95% CI, 0.52–0.99]; $p = 0.044$) or no differences between etanercept versus infliximab (IRR, 1.12 [95% CI, 0.81–1.55]; $p = 0.481$).

Considering only RA patients, the SIAE incidence for TNFi versus controls was 43 per 1000 patient/years (95% CI, 37–50) versus 14 per 1000 patient/years (95% CI, 9–20; adjusted IRR, 3.06; $p < 0.001$). Adalimumab showed lower SIAE IR compared with infliximab, 29 per 1000 patient/years (95% CI, 22–39) versus 55 per 1000 patient/years (95% CI, 43–70; adjusted IRR, 0.52 [95% CI, 0.35–0.76]; $p = 0.001$). There was no statistically significant difference between etanercept and infliximab (adjusted IRR, 0.84 [95% CI, 0.59–1.21]; $p = 0.353$). Subsequent TNFi treatment confirmed a tendency toward a higher SIAE rate when compared with the first, 50 per 1000 patient/years (95% CI, 37–68) versus 41 per 1000 patient/years (95% CI, 34–48), but without statistical significance (adjusted IRR, 1.19 [95% CI, 0.84–1.70]; $p = 0.333$). The SIAEs IR for non-TNFi bDMARDs prescribed as the first biologic was 23 per 1000 patient/years (95% CI, 11–48). Serious infectious adverse events, in all groups, were statistically associated with baseline age, sex, corticosteroid use, or smoking status, but surprisingly not with disease duration or diabetes.

All RA subgroups (TNFi, non-TNFi, and controls) had the highest frequency of serious infections in the respiratory and urinary tracts, as well as SpA patients on TNFi. Spondyloarthritis controls registered only serious infections of the urinary tract. No central nervous system infection was reported in any group. Detailed data are shown in Table 3.

As to the outcome of the 154 serious infections events registered during the first biologic treatment, 124 were classified as recovered without sequelae, 13 as recovered with sequelae, 16 as not recovered, and one as fatal.

There were only 3 fatal infectious events registered, all of which were in RA patients exposed to non-TNFi bDMARDs, and were possibly related to the treatment, corresponding to an IR of 3 per 1000 patient/years (95% CI, 0–23). Of note, 2 of 3 occurred in patients exposed to a non-TNFi biologic but with a previous exposure to a TNFi.

## DISCUSSION

The higher risk of SIAEs in patients using biologic agents is well recognized in all rheumatic conditions. However, most of the registry studies data are from European and North American countries.[7,8] Furthermore, SIAE data in SpA are scarce. This is the first study focusing on SIAEs in RA and SpA on bDMARDs in a Latin American country, demonstrating that the safety profile is similar to that defined by registries in other parts of the world.

Registries reflect the timeline of bDMARDs availability in a particular country. The Brazilian Public Health System covers 100% of the population and made available adalimumab, etanercept, and infliximab first, for RA and SpA.[10,11] For that reason, the large majority of our patients on biologics were using 1 of these 3 medications.

**TABLE 3.** Serious Infectious Adverse Events IR Comparing Biologics and Controls in RA and SPA

| | RA | | | | SpA | | |
|---|---|---|---|---|---|---|---|
| | First TNFi | Subsequent TNFi | Controls | Non-TNFi | First TNFi | Subsequent TNFi | Controls |
| Patients/year | 3102 | 819 | 1971 | 303 | 1967 | 410 | 122 |
| Skin/soft tissue | 7 (5–11) | 9 (4–18) | 1 (0–4) | 0 | 4 (2–7) | 5 (1–20) | 0 |
| Respiratory | 14 (11–9) | 18 (11–30) | 5 (2–9) | 7 (2–26) | 5 (3–9) | 20 (10–39) | 0 |
| Urinary | 13 (9–7) | 10 (5–20) | 4 (2–7) | 7 (2–26) | 3 (1–7) | 20 (10–39) | 33 (12–87) |
| Osteoarticular | 2 (1–4) | 4 (1–11) | 3 (1–6) | 3 (0–23) | 0 | 0 | 0 |
| Other infections | 5 (3–8) | 10 (5–20) | 3 (1–6) | 7 (2–26) | 4 (2–8) | 5 (1–20) | 0 |

Non-TNFi: abatacept, rituximab, and tocilizumab.

Incidence rates per 1000 patient/years (95% CI).

When patients with RA and SpA exposed to TNFi were considered, a higher incidence of serious infections was found, with an adjusted IRR of 2.96 versus sDMARDs. This increased risk is consistent with Spanish (BIOBADASER), Argentinian (BIOBADASAR), and Mexican (BIOBADAMEX) registry studies.[12–14] BIOBADASAR, compared with their internal control group on sDMARDs, found an SIAE IRR of 1.66 (95% CI, 1.38–2.0; $p < 0.05$) (unpublished observations). BIOBADAMEX also found a higher frequency of adverse events in the TNFi group, with infections being the most prevalent cause.[14]

We found a statistically significant increased risk of SIAEs with a subsequent versus first TNFi (adjusted IRR, 1.55). Given that we could not find similar published data to verify our findings, more research is needed on this point. However, some indirect data from the literature make our findings plausible. Although a study from BIOBADASER did not focus on infections, it showed not only a lower drug survival rate for a second TNFi treatment but also that adverse events were an important reason for drug discontinuation.[15] It is important to emphasize that, in this mixed RA-SpA group, no relevant differences in SIAEs were found between adalimumab and infliximab (IRR, 0.71) or etanercept and infliximab (IRR, 1.12).

Our internal cohort of patients treated with sDMARDs comprises 92% of RA patients. Therefore, we recognize that our most consistent data came from analyzing treatments in RA. In these patients, a 3.06-fold greater risk of SIAEs was found in TNFi group (43 per 1000 patient/years vs 14 per 1000 patient/years for controls). This statistically significant increase of frequency of serious infections in the TNFi group was also seen in other longitudinal studies.[16–20] The German registry found 6.42 per 100 patient/years for etanercept, 6.15 per 100 patient/years for infliximab, and 2.28 per 100 patient/years for controls.[16] The REAL Japanese registry showed 6.42 and 2.64 per 100 patient/years for TNFi and controls, respectively.[17] The British registry demonstrated a very similar IR in the TNFi group (42 per 1000 patient/years) but a higher IR of SIAEs in controls (32 per 1000 patient/years).[18]

Our study showed that a first non-TNFi biologic had a lower frequency of SIAEs than the first TNFi (23 vs 41 per 1000 patient/years). At the moment, few registry data about non-TNFi and infections are available. We could find one study with tocilizumab and one with rituximab versus TNFi that showed a higher IR of serious infections with the non-TNFi (10 vs 3.03 and 11 vs 3.1 per 100 patient/years, respectively).[21,22] It is important to consider that our data include abatacept, which could be, at least partially, responsible for the finding that the first non-TNFi biologic had a lower SIAE frequency than the first TNFi in our study population. Noticeably, a recent meta-analysis of randomized controlled trials and long-term extension studies with biologics in RA, reported an IR of SIAEs per 100 patient/years of 4.9 for TNFi, 5.45 for tocilizumab, 3.72 for rituximab, and 3.04 for abatacept.[23] In RA patients, adalimumab was associated with a lower SIAE IR compared with infliximab (IRR, 0.52), whereas no significant difference was found between etanercept and infliximab. In contrast, Lampropoulos et al[19] demonstrated a trend toward higher risk of serious infection with adalimumab, although not statistically significant, Galloway et al[18] showed no difference in SIAEs between adalimumab, infliximab, and etanercept, whereas van Dartel et al[24] found a statistically significant lower risk of serious infections among patients on etanercept therapy. These heterogeneous findings may be due to patients' individualized drug prescription at each study site.

Spondyloarthritis patients on TNFi had half the SIAE risk in relation to RA patients receiving the same treatment (IRR, 0.5) but statistical differences disappear after adjusting the data for age, sex, disease duration, corticosteroids intake, diabetes, and smoking (IRR, 0.96). Few data comparing infections in SpA and RA patients on biologic drugs are available. A lower SIAE incidence in SpA versus RA had been found in a meta-analysis of randomized controlled trials and in a cohort study, compared with literature data.[25,26]

In our study, the most frequent site of infection in RA patients, for both TNFi and controls, was the respiratory tract, followed by the urinary tract and skin/soft tissue. The respiratory tract was the predominant SIAE location in the majority of the studies.[16,17,20,24,27] Skin/soft tissue infections were more frequent in several other registry studies than they were in BIOBADABRASIL.[16,17,19,24,27,28] Spondyloarthritis patients on TNFi therapy had more SIAEs in the respiratory tract, as did the Wallis et al[26] cohort.

In RA, baseline disease duration and diabetes were not associated with serious infections risk in BIOBADABRASIL. Otherwise, Curtis et al[27] has found that diabetes was an independent risk factor to develop infections requiring hospitalization. Age was associated with SIAEs as well, in agreement with data from the United Kingdom, Japan, and the United States.[17,18,27] Corticosteroid intake was associated with SIAEs. We could not further explore this finding because no information on dosage is available in our dataset. Two American studies showed an association with prednisone use greater than 10 mg daily.[20,27]

Fatal infectious adverse events were rare and occurred only in RA patients on non-TNFi, although this group had a lower SIAE IR. In patients on tocilizumab, Sakai et al[21] found a nonstatistically significant higher risk of overall fatal events, when compared with TNFi.

Our study has relevant strengths. Our data are derived from a registry within an accurate methodological framework and a rigid quality control. An internal parallel control group is another

strong point of our database. Moreover, the leadership of the project by the BSR constitutes a guarantee of scientific autonomy. This study shares the same limitations of some others based on registry data. The main one is that the inclusion of patients and events is at principal investigator discretion, being a potential source of bias. In addition, our database covers only a small proportion of patients using biologics in a continental country, namely, Brazil. Another limitation is the lack of information about background corticosteroids and sDMARDs dosage and exposure time for patients in bDMARDs.

## CONCLUSIONS

In BIOBADABRASIL, biologic drugs, especially the subsequent TNFi, were associated with a higher risk of serious infections compared with synthetic DMARDs. Spondyloarthritis showed a tendency toward a lower risk than RA, but it was not proven in our study. Corticosteroid intake and age represented risk factors for SIAEs, whereas diabetes did not. Even if biologic therapy in Brazil, generally, seems to be as safe as it is in other countries, constant monitoring is required to follow the safety profile of drugs in the clinical setting of rheumatic conditions.

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