Rheumatol Int (2014) 34:953–961
DOI 10.1007/s00296-014-2945-y

ORIGINAL ARTICLE

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

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Received: 2 November 2013 / Accepted: 2 January 2014 / Published online: 11 January 2014

Abstract Data on infections in patients exposed to biologic therapies are mainly focused on rheumatoid arthritis (RA). Little is known about the safety profile in other immune-mediated connective tissue diseases (ICTD). The purpose of this study was to describe and to compare the risk of serious infections (SI) in patients with RA and other ICTD on anti-TNF or rituximab and to identify predictors of SI. We analyzed RA or other ICTD patients on anti-TNF or rituximab included in the Spanish registry BIOBADASER 2.0 (2000–2011). For each disease group, incidence rate (IR), mortality rate (MR) and IR ratio (IRR) of SI with 95 % CI were estimated. Risks were then standardized by age and sex to the general population. Risk factors for SI were assessed by Poisson regression models. A total of 3,301 patients on anti-TNF ($n = 3{,}166$) or rituximab ($n = 135$), of which 176 (5 %) had ICTD other than RA, were analyzed. IR of SI was higher in non-RA ICTD than in RA, with an IRR of 3.15 (95 % CI 1.86, 5.31) before adjustment and 1.96 (95 % CI 1.06, 3.65) after adjustment for age, comorbidity and corticoid use. Mortality due to infections was higher in ICTD although it did not reach statistical significance. Age, disease duration, comorbidities, corticosteroids and ICTD different to RA were all independently associated with SI. Patients with ICTD other than RA are at a high risk of SI when prescribed anti-TNF or rituximab, partly due to the excess comorbidity and immunosuppressive co-treatment, but also to the inflammatory disease. When evaluating the risk/benefit ratio of off-label medications in ICTD patients, age, comorbidities and corticoid use should carefully be taken into account, applying adequate preventive measures.

Keywords Serious infections · Anti-TNF · Rituximab · Rheumatoid arthritis · Immune-mediated connective tissue diseases

On behalf of the BIOBADASER 2.0 Study Group.

Please refer the "Appendix" section for BIOBADASER 2.0 study group members.

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Introduction

Serious infections (SI) are one of the dreariest adverse events (AE) of biologic therapies. National and international guidelines cover aspects related to SI, such as how to suspect, prevent and treat them [1–3]. Most recommendations are directed toward the prevention or early detection of AE in rheumatoid arthritis (RA) and other arthropathies on biologic therapy with approved indications, as most data come from this type of patients. However, in clinical

practice, patients with other conditions [2] are prescribed off-label biologic agents, and it is unclear whether the same risks and recommendations would apply in this latter population.

In this context, some authors have investigated whether there are differences in safety between the approved uses and off-label uses of biologic therapies. Conti et al. [4] analyzed rituximab-infusion-related reactions in RA and systemic lupus erythematosus (SLE) patients. Carmona et al. [5] described and compared the safety and retention rate of anti-TNF between RA, ankylosing spondylitis (AS) and other conditions without approved indications, showing that, in general, AE occur more frequently among off-label uses than approved ones.

On the other hand, infections in patients without RA and exposed to biologics have not been extensively studied. It might be useful to know whether there are differences in the type and the rate of infections between a typical immune-mediated connective tissue disease (ICTD) like RA and other ICTD. As the underlying pathogenesis of the diseases may impair different immune cells, this could lead to different types of infections and risks. Therefore, these patients might receive specific recommendations regarding infections.

In the present report, we describe and compare the risk of SI in RA and other ICTD patients on anti-TNF or rituximab from the BIOBADASER registry. In addition, we assess predictors of infections.

Methods

BIOBADASER is a national drug safety registry of patients with rheumatic diseases starting treatment with any biologic and followed thereafter. It was established in February 2000 and it has been described in detail previously [5]. BIOBADASER 2.0 is an adaptation made in 2006, which includes updated information on all patients from 14 large public hospitals throughout Spain, to facilitate monitoring and to increase data reliability. The registry covers roughly a fourth of all rheumatic patients on biologics in Spain. Briefly, patients entering the registry are followed up prospectively and evaluated at the time an AE or a change in the biologic therapy occurs. The following data are collected online and systematically by physicians: (1) patient's data including gender, date of birth, diagnosis, date of diagnosis and comorbidities; (2) data on treatment including types of biologics and dates of initiation and discontinuation, concomitant antirheumatic treatment and tuberculosis prophylaxis treatment; and (3) data on AE, including date of occurrence, type and classification of AE according to the Medical Dictionary for Regulatory Affairs (MedDRA) [6], severity and outcome.

For the assessment of consistency and quality, the database is constantly monitored online, and once a year participating units are advised to check the information on all patients and update it accordingly. Audits reflected a 10 % underreporting in major variables that has been systematically corrected upon detection. Additionally, a random sample of patients is selected and audited in situ in all 14 centers annually. The registry protocol and materials of BIOBADASER 2.0 are available at http://biobadaser.ser.es/biobadaser/eng/index.html and were approved by the Ethics Review Committee of the Hospital Ramon y Cajal (Madrid) acting as reference committee. Starting from January 2008, all patients signed an informed consent that includes an agreement to be contacted by telephone to inquire about vital status and hospital admissions.

Study groups and case definition

For this analysis, we selected all adult patients on anti-TNF or rituximab as first biologic with one of the following ICTD: RA, mixed connective tissue disease (MCTD), scleroderma, SLE, polymyositis, dermatomyositis, recidivant polychondritis, Sjögren's syndrome, Still's disease, vasculitis or overlaps that were included in BIOBADASER 2.0. Patients were further classified into "RA" and "other ICTD."

An SI was defined as any AE that was (1) classified under system organ class (SOC) "Infections and infestations" or(2) described as either "serious" or "fatal" by the treating physician or leads to hospitalization or death.

Exposure

Time of exposure is considered from the beginning of therapy to date of the last administration plus twice the half-life for the anti-TNF [a week for etanercept, 2 months for infliximab, a month for adalimumab] and a year for rituximab. Observation spans from entry into the cohort (beginning of therapy) to censor date (last visit in a lost-to-follow-up patient or treatment discontinuation date), death or July 12th 2011, whichever occurred first. In this analysis, we only considered first biologic to avoid the burden of immunosuppression with sequential use of biologics.

A sensitivity analysis was performed for the at-risk window during which events can be attributed to the drug by two models, one in which events were attributed to the drug if they occurred during the exposure period and another one in which events were attributed to the drug if they occurred within the exposure time plus a lag window of 3 months beyond that period.

Population data

For standardized rates, we used national data on admissions and health statistics. The hospital discharge records (HDR) is the administrative database containing information on all hospital admissions in centers belonging to or collaborating with the National Health System. Private hospitals (17.1 %) are not included in this database. We retrieved all data from January 1st to December 31st 2009, requesting all admissions related to infections in adults (any admission with an ICD-9-CM code 001–139, as the main diagnosis). The National Statistics Institute (INE, at http://www.ine.es) provides information on vital statistics in Spain. All deaths related to ICD-9-CM codes 001–139 in adults occurring between January 1st and December 31st 2009, were used to estimate the expected mortality.

Statistical analysis

The patients included were described using descriptive statistics indicated by the type and distribution of variables. Continuous variables are expressed as means with standard deviations or medians with interquartile range, and categorical variables as frequency with percentages. To compare differences at baseline between the two groups, Student's t or the Mann–Whitney U nonparametric test version and Chi-square tests were used.

The incidence rate (IR) of SI per 100 patient-years with 95 % confidence interval (CI) was estimated by group. Then, we estimated the standardized incidence ratio (SIR) as the ratio of observed cases to expected cases in the general population by age and sex. The mortality rate (MR) of SI and the standardized mortality ratio (SMR) with 95 % CI were calculated by the indirect method, stratified by age and gender, using 2009 data for infections mortality from the Spanish population.

Risk factors for SI were investigated by generalized linear regression models assuming a Poisson distribution of the data. Bivariate and multivariate analyses were performed by backward stepwise selection of all variables with a $p < 0.2$ in the bivariate analysis. The following variables were included in the models: gender, age, disease duration, diagnosis, baseline concomitant treatment, comorbidity and biologic type. Results were expressed as IR ratio (IRR) with their 95 % CIs. All analyses were performed using Stata version 11.2 (Stata Corp., College Station, TX 2008).

Results

Baseline characteristics of patients are depicted in Table 1. Overall, 3,301 patients were included, 3,125 (95 %) of whom were RA and 176 (5 %) other ICTD. On average, patients with RA were older and slightly more frequently women, whereas median disease duration was similar, 8 years in both groups. Most frequent diagnoses under other ICTD were vasculitis (36 %), SLE (26 %) and Sjögren's syndrome (11 %). Anti-TNF were more commonly used as first biologic treatment in RA (98 %; 931 etanercept, 1268 infliximab and 851 adalimumab) than in other ICTD (66 %; 20 etanercept, 85 infliximab and 11 adalimumab). Concomitant treatment like methotrexate was used more frequently in RA. However, glucocorticoids, azathioprine, cyclosporine and cyclophosphamide were more commonly used in other ICTD patients. Comorbidity profile did not differ between groups except for renal failure and hepatitis C, which were more frequent in other ICTD, or hypercholesterolemia, which was more frequent in RA patients than in others.

Regarding outcomes, 281 SI occurred during the exposure to anti-TNF and 32 on rituximab. If exposure was defined with a time lag of 3 months (sensitivity analysis), then 337 cases occurred while on anti-TNF and 33 while on rituximab. As the IRR was similar with both analyses, all results are herein presented with a lag window of 3 months for comparability with published studies [7].

The most frequent infections in all patients and treatment group (see Table 2) were lower respiratory tract infections (pneumonia and bronchitis). A microbiological diagnosis was obtained for 148 infections in RA (45 %; 141 anti-TNF and 7 rituximab) and for 20 infections in other ICTD (51 %; 10 anti-TNF and 10 rituximab). Bacteria were the most frequent microorganisms in RA (62 %; 87 anti-TNF and 5 rituximab) as much as in other ICTD (65 %; 6 anti-TNF and 7 rituximab), which exhibited a balanced distribution between gram positive and gram negative. The main non-opportunistic microorganisms that were identified as cause of pneumonia were Streptococcus pneumoniae. Table 2 shows opportunistic pathogens reported and its location of infection by disease and treatment group. There was a higher trend of opportunistic infections in patients treated with anti-TNF, especially in the RA group, being tuberculosis the most frequent. Although we observed a diverse spectrum of non-tuberculosis opportunistic pathogens, viruses (varicella zoster and cytomegalovirus) were more frequent than bacteria (Listeria monocytogenes), fungi (Candida albicans and Aspergillus fumigatus) or parasites (Leishmania). All the opportunistic pathogens identified in other ICTD patients treated with rituximab developed central nervous system infections (JC virus).

The IR of SI by treatment and diagnosis is presented in Table 3, where it is shown that infections are twice as frequent in ICTD as in RA. In addition, the rate of SI and of death due to SI was, in all groups, several times higher than expected as demonstrated by the high SIR and SMR in Table 4. Regarding mortality, 23 (22 in RA) cases

Table 1 Baseline characteristics of the study population

	RA ($n = 3,125$)	ICTD other than RA ($n = 176$)
Mean (SD) age at baseline (years)	54 (14)	43 (16)***
Women [*n* (%)]	2,480 (79)	126 (72)*
Disease duration in years at baseline, median (p25–75)	8 (4–14)	8 (4–13)
Diagnoses [*n* (%)]		
Rheumatoid arthritis	3,125 (100)	–
Mixed connective tissue disease	–	3 (2)
Scleroderma	–	6 (3)
Systemic lupus erythematosus	–	46 (26)
Overlap scleroderma/SLE	–	2 (1)
Polymyositis/dermatomyositis	–	12 (7)
Recidivant polychondritis	–	10 (6)
Sjögren's syndrome	–	20 (11)
Still's disease	–	13 (7)
Vasculitis	–	64 (36)
First biologic treatment [*n* (%)]		
Anti-TNF	3,050 (98)	116 (66)***
Rituximab	75 (2)	60 (34)***
Concomitant antirheumatic drugs [*n* (%)]		
Methotrexate	1,718 (55)	35 (20)***
Glucocorticoids	1,674 (54)	112 (64)**
Azathioprine	21 (1)	22 (13)***
Cyclosporine	17 (1)	13 (7)***
Cyclophosphamide	3 (0)	13 (7)***
Other DMARDs	745 (24)	24 (14)**
Comorbidity and risk factors [*n* (%)]		
Renal failure	48 (2)	8 (5)**
Interstitial lung disease	96 (3)	6 (3)
Previous cancer	46 (1)	2 (1)
Ischemic heart disease	69 (2)	1 (1)
Cardiac failure	30 (1)	1 (1)
Previous hepatitis B infection	70 (2)	2 (1)
Previous hepatitis C infection	26 (1)	5 (3)*
Diabetes	198 (6)	17 (10)
Hypercholesterolemia	418 (13)	14 (8)*
Hypertension	654 (21)	33 (19)
Current smoker	356 (11)	15 (9)
COPD	82 (3)	1 (1)

RA rheumatoid arthritis, *SD* standard deviation, *DMARDs* disease-modifying antirheumatic drugs, *COPD* chronic obstructive pulmonary disease, *SLE* systemic lupus erythematosus, *ICTD* immune-mediated connective tissue diseases

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

were fatal with anti-TNF and 2 (1 in RA) with rituximab. In Fig. 1, we represent the incidence of SI over the first 2 years of the biologic agent. Incidence is higher in other ICTD patients compared to RA patients, especially in the first 12 months. Also, rituximab-treated patients are more likely to suffer an infection in the first 12 months compared to anti-TNF patients.

Risk factors for SI are shown in Table 5. Univariate analysis revealed that clinical characteristics of the disease, comorbidity, concomitant and biologic treatment were all associated with SI. In the final multivariate model—adjusted for all significant and clinically relevant variables—a higher age and disease duration were associated with SI, as well as COPD, interstitial lung disease, renal failure and hypertension. Corticoid use was also a risk factor for infections, whereas methotrexate use appeared inversely associated. Confirming our hypothesis, having an ICTD other than RA was associated with an SI even after adjustment. Compared to infliximab, other anti-TNF had significantly less SI, even after adjustment.

Table 2 Opportunistic pathogens in serious infections by first biologic therapy and the total number of infections by location (highlighted in bold)

Infection type	RA		ICTD—other than RA	
	Anti-TNF	Rituximab	Anti-TNF	Rituximab
Lower respiratory airways	**118 (37)**	**10 (63)**	**9 (41)**	**7 (41)**
Cytomegalovirus	1	–	–	–
Varicella zoster	1	–	–	–
Mycobacterium tuberculosis	14	–	1	–
Mycobacterium abscessus	–	1	–	–
Aspergillus fumigatus	1	–	2	–
Candida albicans	–	1	–	–
Skin and soft tissue	**46 (15)**	**1 (6)**	**2 (9)**	–
Varicella zoster	6	–	–	–
Osteoarticular	**29 (9)**	–	**1 (5)**	–
Mycobacterium tuberculosis	2	–	–	–
Upper respiratory airways	**25 (8)**	–	**2 (9)**	–
Aspergillus niger	–	–	1	–
Urinary tract	**25 (8)**	**3 (19)**	**1 (5)**	**4 (24)**
Miscellaneous	**25 (8)**	**1 (6)**	**1 (5)**	**3 (18)**
Listeria monocytogenes	1	–	1	–
Cytomegalovirus	2	–	–	–
Varicella zoster	1	–	–	–
Candida albicans	4	–	–	–
Leishmania spp	1	–	–	–
Gastrointestinal	**19 (6)**	**1 (6)**	**6 (27)**	–
Mycobacterium tuberculosis	1	–	–	–
Hepatic, peritoneal, lymph node, or disseminated tuberculosis	17 (5)	–	–	–
Mycobacterium tuberculosis	17	–	–	–
Cardiac	**6 (2)**	–	–	–
Central nervous system	**5 (2)**	–	–	**3 (18)**
Listeria monocytogenes	2	–	–	–
JC virus	–	–	–	2
	315 (100)	**16 (100)**	**22 (100)**	**17 (100)**

Results are expressed as number and percentage (%) or as number (opportunistic infections). Microbiological diagnosis was obtained for 168 infections of a total 370

RA rheumatoid arthritis, *ICTD* immune-mediated connective tissue diseases

Discussion

Our analysis describes the rate of SI in ICTD exposed to anti-TNF and rituximab, and in particular, it compares the rates between RA, an approved indication, and other ICTD, showing that in all cases, but especially in non-RA ICTD, the rate of SI is elevated.

In spite of conventional therapy, ICTD usually have severe flares and develop life-threatening clinical manifestations. In this case, patients may benefit from off-label prescribing to control disease activity [8]. However, off-label prescriptions may pose a challenge to safety, especially when using biologic therapies, which modulator effects on immunological molecules are still only partially understood, and also when using them in diseases with complex immunological interactions. Our hypothesis was that infections—and probably specific types of infection—might be increased.

In a previous analysis of BIOBADASER, we reported a significant increase in the rate of AE in general—and in particular of infections of any severity and type—that was higher in ICTD compared to RA, all exposed to anti-TNF therapies [5]. In the present analysis, we have studied only SI and have studied them in depth regarding locations and types, as well as risk factors; in addition, we have included information not only on anti-TNF exposure but also on rituximab.

The rates of SI in RA exposed to anti-TNF in our study are similar to those from other registers, such as the British

Table 3 Incidence rate of serious infections by first biologic therapy and risk comparison between rheumatoid arthritis and other immune-mediated connective tissue diseases

	Anti-TNF	Rituximab
ICTD—other than RA		
Serious infections	22	17
Patient-years	290	99
IR per 100 patient-years (95 % CI)	7.6 (5–11.5)	17.1 (10.7–27.6)
RA		
Serious infections	315	16
Patient-years	10,242	146
IR per 100 patient-years (95 % CI)	3.1 (2.8, 3.4)	11 (6.7, 17.9)
IRR other ICTD versus RA	2.47 (1.60, 3.80)***	1.57 (0.79, 3.10)

Exposure spans from first dose to 3 months after the last dose or until a serious infection occurred

IRR incidence rate ratio, *CI* confidence intervals, *ICTD* immune-mediated connective tissue diseases *RA* rheumatoid arthritis

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Table 4 Standardized incidence ratio (SIR) and mortality ratio (SMR) of serious infections by type of first biologic therapy and disease

	SIR (95 % CI)		SMR (95 % CI)	
	Anti-TNF	Rituximab	Anti-TNF	Rituximab
Rheumatoid arthritis				
Men	16 (13, 20)	32 (1, 179)	8 (3, 17)	49 (1, 271)
Women	21 (19, 24)	186 (106, 302)	8 (4, 13)	0 (0, 156)
Immune-mediated connective tissue diseases other than RA				
Men	40 (14, 86)	82 (44, 140)	0 (0, 320)	0 (0, 1,400)
Women	72 (41, 117)	91 (55, 140)	39 (1, 217)	106 (3, 591)

SIR standardized incidence ratio, *SMR* standardized mortality ratio, *CI* confidence intervals

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

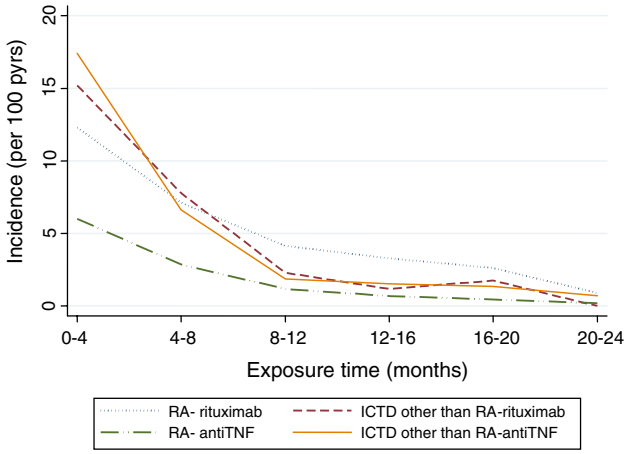

Fig. 1 Risk of serious infections over time. *RA* rheumatoid arthritis, *ICTD* immune-mediated connective tissue diseases, *PYRS* patient-years

register (4.2/100 patient-years) [9]. With regard to rituximab, Curtis et al. [10] reported a higher rate of SI in RA patients exposed to rituximab without biologic use in the previous year, compared to patients who had been previously with other biologic agents [IR of SI by hospitalization was 10.4 (6.3–17.2) vs. 7.1 (4.6–10) per 100 patient-years]. In our study, the rates of SI are higher for rituximab than for anti-TNF, but the risk, in comparison with RA, is reduced when adjusting for comorbidity and other risk factors. Also, the small number of patients on rituximab results in wide confidence intervals, what moves us to be cautious in deriving any conclusions from comparing biologic therapies. Another limitation of our study might be the difference in the measurement of events in the register compared to the measurement in the general population, what may overestimate the problem in patients followed up in registers. However, within groups of the same cohort, comparisons are less of a problem. A few studies evaluate the rate of SI in patients with ICTD on biologic treatment [11–13]. Diaz Lagares et al. estimated an IR of SI of 11.2 and 5.21 per 100 patient-years for rituximab and anti-TNF, respectively, in a prospective cohort of several ICTD other than RA (11). As shown in the multivariate analysis in our study, the increase in the risk with rituximab might be explained by a larger use of rituximab precisely in non-RA ICTD patients, many of which have other risk factors for infections, especially lung and renal problems, and co-treatments such as corticoids.

Adding to what has been reported to other studies regarding mortality by infection in ICTD, be this RA or not, we want to stress that dying of infection is a true risk in this population. Even though the most frequent cause of death is cardiovascular events, the one that remains higher than expected is infections, both in RA and in the rest of ICTD [14–16]. Therefore, our study emphasizes the importance in the use of preventive measures to avoid infections and their complications in ICTD patients and in particular if exposed to anti-TNF or rituximab.

Regarding the site of infections, lower respiratory tract infections (pneumonias) were the most frequent, similar to other cohorts [11], and similar between RA and non-RA ICTD. As it occurs in the general population, the bacteria were the most frequent cause of infections including those of the lower respiratory tract. Therefore, vaccination against Streptococcus pneumoniae before biologic therapies in ICTD patients might be a justified preventive measure. In relation to opportunistic infections, in RA and anti-TNF group more cases were reported. Although the effect of TNF blocking increases the risk of opportunistic

Table 5 Risk factors for serious infections: results from the univariate and full multivariate adjusted model

	Serious infections (*n*)	Patient-years	Univariate IRR (95 % CI)	Multivariate IRR (95 % CI)
Risk factors				
Women	271	8,483	0.74 (0.54, 1.01)	0.89 (0.65, 1.22)
Age (years)			1.04 (1.03, 1.05)***	1.03 (1.02, 1.04)***
Disease duration (years)			1.03 (1.01, 1.04)***	1.02 (1.01, 1.03)**
Diagnoses				
Rheumatoid arthritis	331	10,388	1 (Reference)	1 (Reference)
ICTD other than RA	39	389	3.15 (1.86, 5.31)***	1.96 (1.06, 3.65)*
Comorbidity				
Interstitial lung disease	37	256	4.56 (2.94, 7.06)***	2.88 (1.93, 4.3)***
Renal failure	28	173	5.02 (2.84, 8.88)***	1.87 (1.02, 3.41)*
Previous cancer	14	140	3 (1.15, 7.82)*	–
Ischemic heart disease	20	225	2.68 (1.34, 5.38)**	–
Cardiac failure	12	73	4.92 (2.39, 10.12)***	–
Previous hepatitis B	17	254	1.99 (1.01, 3.95)*	–
Previous hepatitis C	5	94	1.56 (0.52, 4.7)	–
COPD	46	242	6.19 (3.91, 9.81)***	3.53 (2.25, 5.53)***
Diabetes	47	566	2.63 (1.79, 3.85)***	–
Smokers	58	1,139	1.57 (1.01, 2.44)*	–
Hypercholesterolemia	78	1,389	1.81 (1.28, 2.55)***	–
Hypertension	146	2,078	2.73 (2.05, 3.62)***	1.65 (1.22, 2.23)***
Concomitant treatment				
Methotrexate	175	5,835	0.76 (0.59, 0.99)*	0.69 (0.52, 0.9)**
Azathioprine	4	109	1.07 (0.4, 2.83)	
Cyclosporine	12	104	3.44 (1.47, 8.08)**	
Cyclophosphamide	2	25	2.37 (0.49, 11.39)	
Other DMARDs	110	2,291	1.57 (1.18, 2.09)**	–
Corticosteroids	231	5,490	1.6 (1.22, 2.1)***	1.74 (1.32, 2.28)***
Biologic treatment				
Infliximab	218	3,197	1 (Reference)	1 (Reference)
Etanercept	68	4,709	0.46 (0.33, 0.65)***	0.48 (0.34, 0.68)***
Adalimumab	51	2,626	0.42 (0.30, 0.59)***	0.45 (0.32, 0.64)***
Rituximab	33	245	2.91 (1.66, 5.09)***	1.38 (0.78, 2.43)

IRR incidence rate ratio, *RA* rheumatoid arthritis, *COPD* chronic obstructive pulmonary disease, *DMARDs* disease-modifying antirheumatic drugs, *CI* confidence intervals, *ICTD* immune-mediated connective tissue diseases

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

infections, this result may also be influenced by the fact that more patients were on anti-TNF than on other therapies. In addition, tuberculosis infections occurred mainly on the early years of the register—before 2002—when most patients were RA on anti-TNF drugs. Afterward, systematic screening and prophylaxis of latent tuberculosis reduced dramatically the rate of tuberculosis [17].

We found different infection patterns in central nervous system. In RA patients treated with anti-TNF, all opportunist infections were produced by Listeria, whereas in non-RA ICTD patients treated with rituximab, those were caused by JC virus. Listeriosis has been associated with anti-TNF treatment but not with rituximab, since TNF blocking alters the granulomatous response [18]. The probability of developing progressive multifocal leukoencephalopathy (PML) might be due to several added factors. Firstly, the use of some synthetic immunosuppressants (azathioprine, cyclosporine, mycophenolate mofetil, tacrolimus and cyclophosphamide) has been associated with PML (19). Secondly, rituximab, through an as-yet-undefined mechanism, might facilitate reactivation of JC virus in the form of PML [19, 20]. Lastly, SLE patients appear to have a particular susceptibility to the development of PML [20]. Our two patients with PML met all these factors.

To better design preventive strategies, it is also important to study risk factors for SI. Age, disease duration,

concomitant corticoids and comorbidities are consistent risk factors for infections in RA with or without exposure to biologic treatment [21–23], and in other ICTD like SLE and polymyositis/dermatomyositis [24–26]. What our study adds might be the influence of the underlying disease: The risk of serious infection is higher in other ICTD than in RA, independently of age, comorbidity and concomitant therapy. This finding may be related to the association between high levels of inflammation and risk of infections. Very probably, those patients with ICTD other than RA who are prescribed biologic therapy are much worse off in terms of inflammation and damage than others, as it happened with the first patients with RA that we started on biologics.

Conclusions

In conclusion, patients with ICTD other than RA are at a high risk of SI when prescribed anti-TNF or rituximab, partly due to the excess comorbidity and immunosuppressive co-treatment, but also inherent to the inflammatory disease. When evaluating the risk/benefit ratio of off-label medications in ICTD patients, age, comorbidities and corticoid use should carefully be taken into account, applying all preventive measures at hand. Additionally, close follow-up and education on how to detect infections must be instituted. Early suspicion of infection in front of unclear events will be key to avoid unnecessary deaths.

Acknowledgments The authors thank the dedication to BIOBADASER of Angel Guillen, monitor, and Juan Manuel Barrio, technology assistant. BIOBADASER is supported by the Research Unit of the Spanish Foundation for Rheumatology (FER), the Spanish Agency for Medicines and Medical Devices (AEMyPS) and the Spanish Society of Rheumatology (SER). Grants in approximately equal amounts (all under 25,000€/year) from Roche, Abbott, BMS, MSD and Pfizer contribute to the support of the registry. This work was partially supported by RETICS Program, RD08/0075 (RIER) from Instituto de Salud Carlos III (ISCIII). The pharmaceutical companies and RETICS Program had no role in this study. All researchers in this work are independent from funders. In the collaboration contracts signed by the Spanish Society of Rheumatology, independence of the BIOBADASER registry has been affirmed with respect to the analyses as well as the diffusion of data and results.

Conflict of interest TCI and LC had financial relationships with Roche, Abbott and Pfizer; ELS had financial relationships with Roche, Abbott; SMF had financial relationships with Roche, Abbott, Pfizer, MSD and GSK. No other relationships or activities that could appear to have influenced the submitted work.

Appendix: BIOBADASER 2.0 study group members

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