Risk of hospitalisation for serious bacterial infections in patients with rheumatoid arthritis treated with biologics. Analysis from the RECord linkage On Rheumatic Disease study of the Italian Society for Rheumatology

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Abstract

Objective
The aims of this study were to define the risk of serious bacterial infections in patients receiving specific biological disease-modifying anti-rheumatic drugs (bDMARDs) and evaluating the effect of concomitant synthetic DMARDs (sDMARDs) in a large population-based sample of rheumatoid arthritis (RA) deriving from an administrative health database.

Methods
Data were extracted from health databases of Lombardy Region, Italy (2004–2013), as a part of the RECord-linkage On Rheumatic Diseases (RECORD) study. Patients with RA treated with approved bDMARDs were included. Hospitalisations for bacterial infections were evaluated by hospital discharge forms. The association between drug exposure and infections was assessed by survival models, with time-dependent covariates. Results are presented as hazard ratios (HR) and 95%CI, crude and adjusted for pre-specified confounders (sex, age, disease duration, Charlson Comorbidity Index, previous biologics, previous infections, use of methotrexate, leflunomide, corticosteroids, non-steroidal anti-inflammatory drugs).

Results
4,656 RA patients with at least one bDMARD prescription were included, for a total of 7,601 biological courses; 3,603 (77.4%) women with a mean (SD) age of 55.8 (12.7) years. Crude incidence rate of hospitalised infection ranged from 0.14 to 2.95 per 1000 person-years. After multivariable adjustment, abatacept users (HR 0.29, 95%CI 0.10–0.82) had significantly lower risk of infections compared to etanercept. Concurrent treatment with methotrexate (0.72, 0.52–0.99) reduced the overall risk of infection while glucocorticoids increased it (1.09 per mg/day, 1.06–1.11).

Conclusion
In RA patients treated with bDMARDs, abatacept was associated with the lowest risk of infections; overall risk was mitigated by concomitant methotrexate and increased by glucocorticoids in a dose-dependent manner.

Key words
biological disease-modifying anti-rheumatic drugs, rheumatoid arthritis, bacterial infections, synthetic disease-modifying anti-rheumatic drugs

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Introduction

The introduction of biologic disease-modifying anti-rheumatic drugs (b-DMARDs) for the treatment of rheumatoid arthritis (RA) has allowed a better disease control in patients non-responsive to synthetic DMARDs (sDMARDs), leading to better disease outcomes (1). However, the molecular targets addressed by these drugs, such as tumor necrosis factor-α (TNF-α) and lymphocytic function, are involved in immune response and resistance against infections. Their use has therefore been related to an increased risk of infections, including intracellular and opportunistic infections, which might be due to several factors (2–5). Patients with RA have an increased infectious risk compared to general population (6, 7) that is related to disease characteristics, such as extra-articular manifestations, implying a more severe disease, and comorbidities (8). Since bDMARDs are frequently prescribed to patients with a more severe disease, a baseline higher risk of infection might be present in this group; at the same time, disease-independent baseline relative risk of infection (*e.g.* patients with a lower number of comorbidities, patients treated with treat-to-target approach (9)) could drive bDMARDs prescription, leading to a complex relationship between indication and contraindication biases. In keeping with these considerations, the comparison with patients on sDMARDs-monotherapy yielded contrasting results, with some studies confirming the presence of a consistent increase in risk (10), especially in the first months of bDMARD treatment (11), whilst other studies showed only a moderately increased (12) or a comparable risk (13). Also, differences might exist between the available drugs, with abatacept (ABA) being related to a lower risk of serious infections compared to other bDMARDs (14, 15).
sDMARDs do not seem to lead to more infections, as suggested by the results of large observational studies evaluating sDMARDs monotherapies (16, 17), with some reports of a decreased rate of infections in patients on methotrexate (MTX) and hydroxychloroquine (HCQ) (14); nevertheless the presence of comorbidities or a higher disease activity correlate with higher number of infections also in this patients (18). Finally, glucocorticoids (GCs) have consistently been related to increasing the risk of infections (19), also in patients receiving bDMARDs, with a dose-related effect (20, 21).

In clinical practice, the management of patients with RA frequently implies the administration of multiple concurrent treatments but the amount of information on the impact of co-medication during treatment with bDMARDs is limited. Although it has been demonstrated that patients receiving MTX in association with TNF-inhibitors tend to discontinue treatment less frequently because of loss of efficacy (22) and of adverse events (23) and that the rate of discontinuation is not significantly different in patients receiving MTX or leflunomide (LEF) co-medication (24, 25), the precise role of concurrent therapies on adverse events – infections in particular – in patients receiving bDMARDs is not clearly established.

In last decade, the use of large administrative health databases (AHD) has emerged as a feasible strategy to study a consistent number of patients for long periods, with the availability of complete data and without loss at follow-up (26, 27).

In this study we aimed to define the risk of serious bacterial infections in patients receiving bDMARDs, evaluating clinical and demographic factors associated with this outcome and exploring the influence of specific biologic agents and the role of concurrent sDMARDs and GCs co-medication in a large population sample deriving from AHD of the Lombardy region in Italy.

Materials and methods
Study design
This is a retrospective cohort study on AHD of Lombardy Region, Italy (>10,000,000 inhabitants).

Ethics approval and consent to participate
Access to the data was granted by the General Directorate of Health for the purpose of the RECORD study proto-

col of analysis, a project promoted by the Italian Society for Rheumatology (SIR), in accordance with national ethical requirements. The protocol was approved by the local ethics committee of the Pavia University Hospital. No specific consent to participate was needed.

Data
Data retrieved from the AHD included demographics (birth date, gender, death date or embarkment), drug prescriptions (Anatomic-Therapeutic Chemical - ATC - code, date of drug delivery, quantity), RA certification by a rheumatologist, outpatient services and hospital discharge forms (HDF) including information on time International Classification of Disease, 9th revision, Clinical Modification (ICD-9-CM) diagnoses and Disease Related Group - DRG - codes for the period between 1st of January 2004 and 31st of December 2013.

Population
Patients with RA were identified through rheumatologist certification of disease (co-payment exemption code 006.714.0), based on its previously demonstrated high specificity (96.39%) and sensitivity (77.08%) for RA recognition (27), following other studies with a similar methodology (28, 29). Patients with RA and at least one delivery of bDMARDs (ABA, adalimumab (ADA), certolizumab (CER), etanercept (ETA), golimumab (GOL), infliximab (INF), rituximab (RTX) and tocilizumab (TCZ)) were included. Different lines of bDMARD treatment were considered. The exposure to non-steroidal anti-inflammatory drugs (NSAIDs), specific sDMARDs – including MTX, LEF, cyclosporine A (CSA), HCQ or sulfasalazine (SSZ) – and daily mean GC dosage (mg per day) were defined by the drug delivery recorded in the administrative database. Number of previous courses of bDMARDs, age at the start of each bDMARD course, the presence of a previous hospitalised infection (in the year before starting the first bDMARD) and the presence of an antibiotic treatment course of at least 14 days occurred in the previous year was also recorded.

Exposure
Exposure to bMDARDs was considered changing during follow-up. A patient was considered exposed to a specific biological treatment from the first prescription of the drug until the last one plus 6 months, to consider the coverage period of a drug also after its withdrawal, or until the first prescription of subsequent drug. Censoring was defined at treatment stop date plus drug coverage or until the start of a new bDMARD or death or at the end of established follow-up. Exposure to a new bMDARD in the same patient was defined as a new bDMARD treatment course.

Outcome
Hospitalisations for the first bacterial infection occurred during the exposition to each bDMARD were evaluated using HDF based on relevant ICD-9-CM codes: ICD-9-CM 049* and 320* are considered for meningitis; 054.3 and 323* for encephalitis; 681*-682* for cellulitis; 421* for endocarditis; 481*-482* for pneumonia; 590* for pyelonephritis; 711* for septic arthritis; 730.0*-730.2* for osteomyelitis and 038* and 790.7 for bacteraemia (30).

Statistical methods
Continuous characteristics are presented as median and interquartile range (IQR) or mean and standard deviation (SD), when appropriate. For proportions, absolute and relative frequencies are reported. The association between bDMARDs exposure and hospitalisation for bacterial infections was assessed by survival models for competing risks (death), with time-dependent covariates (Cox proportional hazard models). Results were presented as hazard ratios (HR) and 95% confidence intervals (95%CI), crude and adjusted for pre-specified confounders (sex, age, disease duration, Charlson Comorbidity Index (31), concomitant use of MTX, LEF, GCs, NSAIDs, number of previous biologics and previous infections). All the analyses were performed using the Stata11 software (STATA Corporation, College Station, Texas, USA) and R Statistical Software (Foundation for Statistical Computing, Vienna, Austria).

Table I. Clinical and demographic features of the population included of 4,656 RA patients.

Demographic characteristics	
Mean age (SD, years)	55.8 (12.7)
Female, n (%)	3603 (77.4)

Clinical characteristic	
Disease duration, n (%)	
≤1 years	1052 (22.6)
>1 to ≤2 years	1137 (24.4)
≥3 to ≤5 years	1090 (23.4)
>5 years	1377 (29.6)
Charlson Comorbidity Index, Mean (SD)	1.24 (0.75)
Serious infections in the previous year, n (%)	24 (0.5)
Antibiotic prescription in the previous year, n (%)	877 (18.8)

Results
A total of 4,656 RA patients who had at least one bDMARD delivery for a total of 7,601 biological treatment courses (exposures), equal to 20,519 person/years (PYs) of exposure, were included. 3,603 were women (77.4 %) with a mean age (SD) at first bDMARD exposure of 55.8 (12.7) years and with modal disease duration of over five years. No missing data nor lost to follow-up were registered, nor expected by design.
A mean (SD) Charlson Comorbidity Index Score equal to 1.24 (0.75) was estimated (Table I). 24 patients (0.5%) had a hospitalised infection in the previous year and 877 (18.8%) a previous course of antibiotic treatment lasting more than 14 days in the past year (Table I).
Of 7,601 treatment courses, 32.4% were with ETA, 22.2% with ADA, 13.7% with INF, 9.5% with ABA, 7.2% with TCZ, 6.7% with RTX, 4.2% with GOL and 4.0% with CER.
Among concomitant immunosuppressive medications, MTX was the most commonly prescribed sDMARD. This combination therapy was observed in 4,942 treatment courses (65% of biological treatment courses), especially in association with TNF-inhibitors. Combination therapy with LEF has been observed in 776 (10.2%) exposures, and a concomitant prescription of another sDMARD (CSA, HCQ or SSZ) was found during exposure to biologics in 21.4% of cases (Table II). We identified 181 hospitalised infec-

Table II. Biological exposures, person-years and concomitant medications.

bDMARDs	All	ETA	ADA	INF	CER	GOL	ABA	RTX	TCZ
Biological treatment courses, n (%)	7,601	2,462 (32.4)	1,687 (22.2)	1,042 (13.7)	306 (4.0)	322 (4.2)	724 (9.5)	507 (6.7)	551 (7.2)
Person years	20,519	8,296	4,851	3,199	406	451	1404	984	928
Mean (SD) number of previous bDMARD	0.64 (1.02)	0.36 (0.70)	0.42 (0.72)	0.28 (0.70)	1.10 (1.52)	1.06 (1.37)	1.36 (1.16)	1.14 (1.22)	1.35 (1.35)
**NSAIDs, n (%)	5,550 (73)	1,864 (75.7)	1,257 (74.5)	832 (79.8)	201 (65.7)	191 (59.3)	476 (65.7)	334 (65.9)	395 (71.7)
**MTX, n (%)	4,942 (65.0)	1,562 (63.4)	1,125 (66.7)	851 (81.7)	184 (60.1)	205 (63.7)	448 (61.9)	258 (50.9)	309 (56.1)
**LEF, n (%)	776 (10.2)	289 (11.7)	205 (12.2)	92 (8.8)	27 (8.8)	29 (9)	58 (8)	37 (7.3)	36 (6.5)
**sDMARD (CSA,HCQ, SSZ), n (%)	1,627 (21.4)	538 (21.9)	345 (20.5)	220 (21.1)	62 (20.3)	82 (25.5)	168 (23.2)	90 (17.8)	122 (22.1)
**Mean (sd) GCs dosage (mg/day)	2.57 (3.66)	2.34 (3.55)	2.42 (3.18)	2.74 (3.9)	2.18 (2.83)	2.53 (4.02)	2.77 (3.35)	3.66 (5.29)	2.73 (3.57)

**Concomitant medications. ABA: abatacept; ADA: adalimumab; CER: certolizumab; ETA: etanercept; GOL: golimumab; INF: infliximab; RTX: rituximab; TCZ: tocilizumab; bDMARDs: biological disease-modifying anti-rheumatic drugs; NSAIDs: non-steroidal anti-inflammatory drugs; sDMARDs: synthetic disease-modifying anti-rheumatic drugs; MTX: methotrexate; LEF: leflunomide; CSA: cyclosporine A; HCQ: hydroxychloroquine; SSZ: sulfasalazine; GCs: glucocorticoids.

tions (68 with ETA, 52 with ADA, 26 with INF, 4 with ABA, CER and GOL, 13 with RTX and 10 with TCZ) yielding to an overall incidence of 8.82 cases per 1000 person/years. The types of infections are shown in Table III. Pneumonia followed by bacteraemia and cellulitis were the most common types of infections observed.

The primary results of the study are described in Table IV and V. Table IV shows the factors associated with hospitalisation with a definite bacterial infection: age at exposure (HR 1.04, 95%CI 1.02, 1.05) and the presence of infections in the previous year (HR 1.52, 95%CI 1.06, 2.18) were related to a significantly increased risk of severe infections, while the female gender was associated with a lower risk (HR 0.68, 95%CI 0.49, 0.94). The concomitant treatment with NSAIDs and sDMARDs (LEF or other sDMARDs) did not result in an increased risk of hospitalisation for bacterial infections while the use of MTX, compared with bDMARD monotherapy, reduced the risk by 28% (HR 0.72, 95%CI 0.52, 0.99). Prednisone equivalent prescription correlates to an increased risk of 9% for each daily mg (HR 1.09, 95%CI 1.06, 1.11).

When directly comparing biologic agents to one another using Cox proportional hazard models, potential confounders were controlled (Table V). Considering ETA as reference, the

Table III. Type of infections reported in our study.

Type of infection	n events/person years	Incidence rate (x 1000) (95%CI)
Pneumonia	61/20,661	2.95 (2.26, 3.79)
Bacteraemia	52/20,711	2.51 (1.88, 3.29)
Cellulitis	27/20,721	1.30 (0.86, 1.90)
Septic arthritis	22/20,746	1.06 (0.66, 1.61)
Osteomyelitis	13/20,764	0.63 (0.33, 1.07)
Pyelonephritis	10/20,740	0.48 (0.23, 0.89)
Meningitis	8/20,762	0.39 (0.17, 0.76)
Encephalitis	3/20,763	0.14 (0.03, 0.42)
Endocarditis	3/20,764	0.14 (0.03, 0.42)

Table IV. Factors associated with hospitalised infection among RECORD RA patients.

	Crude HR (95%CI)	Adjusted HR (95%CI)
Female	0.72 (0.52, 1)	0.68 (0.49, 0.94)
Age (time-related)	1.04 (1.03, 1.05)	1.04 (1.02, 1.05)
Charlson Comorbidity Index	1.36 (1.2, 1.55)	1.14 (0.93, 1.39)
Disease duration		
Disease duration >1 to ≤2 years	1.45 (0.91, 2.33)	1.39 (0.84, 2.30)
Disease duration ≥3 to ≤5 years	1.69 (1.08, 2.66)	1.52 (0.93, 2.47)
Disease duration >5 years	1.50 (0.93, 2.42)	1.63 (0.98, 2.73)
bDMARD (previous)	0.97 (0.81, 1.16)	0.98 (0.79, 1.21)
Infections (year before first bDMARD)	1.51 (1.07, 2.14)	1.52 (1.06, 2.18)
Concomitant medication		
MTX*	0.69 (0.51, 0.95)	0.72 (0.52, 0.99)
LEF*	0.84 (0.49, 1.47)	0.82 (0.47, 1.43)
sDMARDs others* (CSA,HCQ, SSZ)	0.76 (0.39, 1.47)	0.82 (0.42, 1.59)
GCs°	1.09 (1.07, 1.12)	1.09 (1.06, 1.11)
NSAIDs	1.37 (0.89, 2.11)	1.2 (0.77, 1.87)

*compared to bDMARDs monotherapy; °for each increase of 1 mg/day. bDMARDs: biologic disease-modifying anti-rheumatic drugs; sDMARDs: synthetic disease-modifying anti-rheumatic drugs; MTX: methotrexate; LEF: leflunomide; CSA: cyclosporine A; HCQ: hydroxychloroquine; SSZ: sulfasalazine; GCs: glucocorticoids; NSAIDs: non-steroidal anti-inflammatory drugs; HR: Hazard Ratio; CI: confidence interval.

adjusted HR for infection was equal to 0.29 (95%CI 0.10, 0.82) for ABA, while it was not significantly different compared to other bDMARDs.

The adjusted HRs and 95%CI for each bDMARD compared with ETA and the clinical and demographic factors associated with hospitalisation for a defi-

Table V. Events, person years (PYs), crude and adjusted HR for hospitalised infection compared to Etanercept.

Biologic exposure	Events	PYs	Incident rate *1000 PY (95%CI)	Crude HR (95% CI)	Adjusted HR (95%CI)*
Etanercept	68	8296	8.2 (6.4, 10.4)	Ref (1.0)	Ref (1.0)
Adalimumab	52	4851	10.7 (8, 14.1)	1.27 (0.88, 1.82)	1.37 (0.95, 1.96)
Infliximab	26	3199	8.1 (5.3, 11.9)	0.98 (0.62, 1.54)	0.96 (0.60, 1.56)
Certolizumab	4	406	9.9 (2.7, 25.2)	0.93 (0.34, 2.55)	1.31 (0.48, 3.58)
Golimumab	4	451	8.8 (2.4, 22.7)	0.84 (0.31, 2.32)	1.09 (0.37, 3.21)
Abatacept	4	1404	2.8 (0.8, 7.3)	0.3 (0.11, 0.83)	0.29 (0.10, 0.82)
Rituximab	13	984	13.2 (7.0, 22.6)	1.4 (0.77, 2.55)	0.95 (0.48, 1.91)
Tocilizumab	10	928	10.8 (5.2, 19.8)	1.09 (0.56, 2.12)	1.24 (0.59, 2.61)

*Adjusted for pre-specified confounders (gender, age, disease duration, NSAIDs, number of previous bDMARDs, Charlson Comorbidity Index, infections and antibiotic prescription for 14 days in the previous year); HR, hazard ratio; CI, confidence interval.
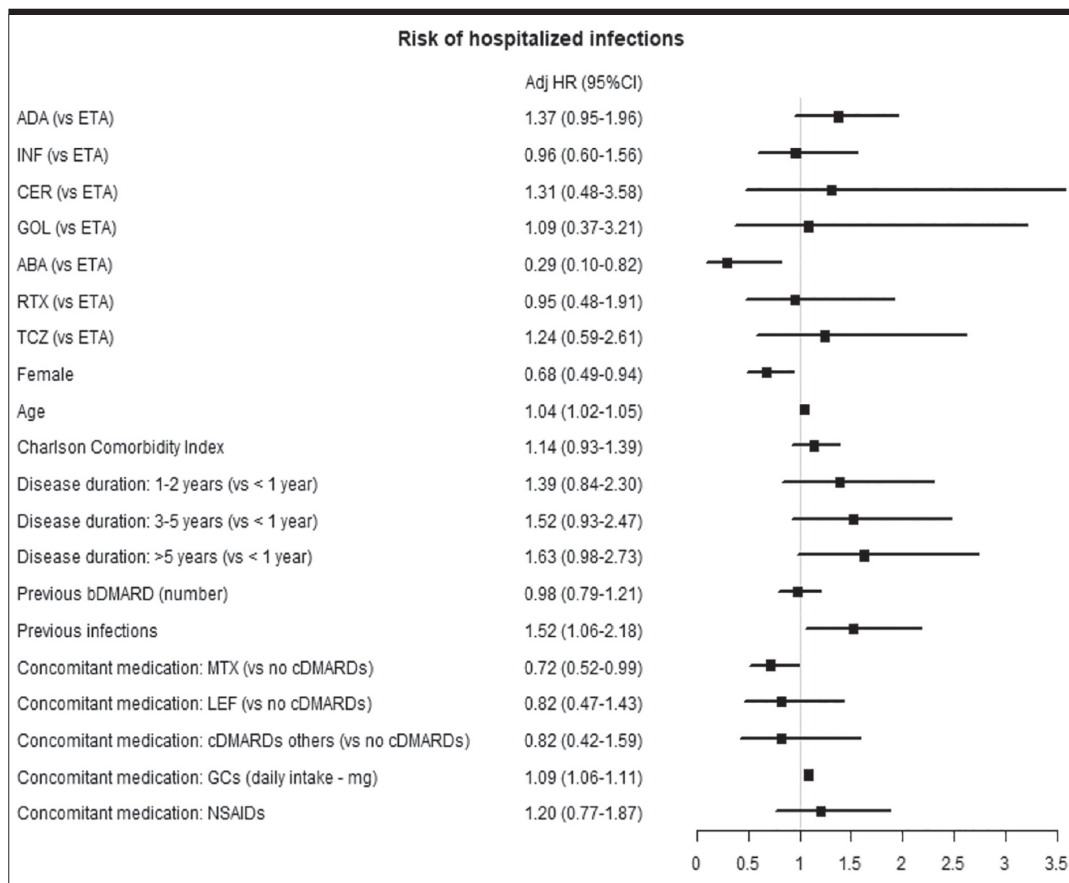
nite bacterial infection are summarised in Figure 1.

Discussion

In this large retrospective cohort, including 4,656 patients with RA treated with bDMARDs with complete data deriving from AHD, the incidence rate for serious infections requiring hospitalisation was 8.82/1000 PYs. The demographical and clinical features of this sample are comparable to those of populations of patients treated with biologics included in large registries (32). Pneumonia and bacteraemia were the most incident infections, consistently with previous observational studies reporting a higher risk of hospitalisation for pneumonia (14, 33).

When examining the predictors of severe infections in a multivariate model, as expected older age and previous severe infections were related to a higher risk. In the adjusted analyses, comorbidities were only marginally associated with infection due to their association with age. On the other hand, women showed a slightly reduced risk. This finding is not supported by previous studies and needs to be tested in different populations (34).

When evaluating the impact of concomitant medications, concurrent treatment with sDMARDs did not lead to an increased risk of infection. On the contrary, MTX was related to a reduction of infectious risk, as already reported in previous studies (23), confirming the benefits of combination treatment over hospitalised bacterial infections. A previous report gave similar results, with patients treated with bDMARDs combined to MTX, alone or with other sDMARDs, experiencing less frequently severe adverse events. A possible explanation for this could be a better control of disease activity resulting in lower number of adverse events related to RA, including infections. Moreover, due to the limited detail in clinical information available in the AHD, channelling bias cannot be fully excluded, with MTX being administered to fitter subjects. In our study, also LEF, CSA, HCQ and SS-

Risk of hospitalized infections

	Adj HR (95%CI)
ADA (vs ETA)	1.37 (0.95-1.96)
INF (vs ETA)	0.96 (0.60-1.56)
CER (vs ETA)	1.31 (0.48-3.58)
GOL (vs ETA)	1.09 (0.37-3.21)
ABA (vs ETA)	0.29 (0.10-0.82)
RTX (vs ETA)	0.95 (0.48-1.91)
TCZ (vs ETA)	1.24 (0.59-2.61)
Female	0.68 (0.49-0.94)
Age	1.04 (1.02-1.05)
Charlson Comorbidity Index	1.14 (0.93-1.39)
Disease duration: 1-2 years (vs < 1 year)	1.39 (0.84-2.30)
Disease duration: 3-5 years (vs < 1 year)	1.52 (0.93-2.47)
Disease duration: >5 years (vs < 1 year)	1.63 (0.98-2.73)
Previous bDMARD (number)	0.98 (0.79-1.21)
Previous infections	1.52 (1.06-2.18)
Concomitant medication: MTX (vs no cDMARDs)	0.72 (0.52-0.99)
Concomitant medication: LEF (vs no cDMARDs)	0.82 (0.47-1.43)
Concomitant medication: cDMARDs others (vs no cDMARDs)	0.82 (0.42-1.59)
Concomitant medication: GCs (daily intake - mg)	1.09 (1.06-1.11)
Concomitant medication: NSAIDs	1.20 (0.77-1.87)

Fig. 1. Risk of hospitalisation for bacterial infections in RA patients treated with biologics. The figure shows the adjusted hazard ratio (HR) and 95%CI for all bDMARDs (abatacept - ABA, adalimumab - ADA, certolizumab - CER, golimumab - GOL, infliximab - INF, rituximab - RTX, tocilizumab - TCZ) compared with etanercept (ETA) and the clinical and demographic factors associated with hospitalisation for bacterial infections.

Zwere not related to an increased risk of infection. Previous researches in this field have indirectly shown conflicting results, with both similar persistence on anti-TNF in combination with either MTX or LEF (25, 35) and higher discontinuation rates with LEF combination (24), although none of these reports considered hospitalised bacterial infections as outcome. Consistently with many studies including both patients on sDMARDs and bDMARDs, concurrent corticosteroid treatment led to higher risks of severe infections (14). However, due to the limited clinical detailed information deriving from the use of AHD, a confounding by indication effect cannot be completely excluded. Thus, more severe patients would be more likely to receive higher corticosteroid dosages.

When examining the risk related to single bDMARDs, considering ETA as reference, patients treated with ABA had a statistically and clinically significant lower risk of serious infections, while no significant differences emerged for the remaining drugs. This finding is partially in keeping with a previous study, based on AHD, reporting a lower risk of hospitalised infections in patients treated with ABA and ETA compared to the remaining biologics in patients with a history of a previous infection (36). More recent evidences also support the safety of ABA in term of risk of hospitalised infections (15, 34). The results of our study confirm this finding in a more generalisable population of patients treated with bDMARDs, which do not carry a higher background risk of infection.

Our results must be interpreted in the context of the study design. First, we explicitly restricted our attention to severe bacterial infections requiring hospitalisation without focusing on opportunistic infections (*i.e.* tuberculosis) and milder infections, diagnosed and treated in the outpatient setting. However, this approach certainly underestimates the incidence of infections but it is recognised as the most specific, able to minimise misclassification due to surveillance bias (37). The diagnosis of infection was based on at least one diagnosis code for infections claims data

in any position, with the possibility of having included infections accidentally recognised during hospitalisations not related to the infection itself. However, this possible overestimation is not likely to differentially misclassify infections in differently exposed patients. The different burden of prescribed bDMARDs (being ETA, ADA and INF the most prescribed ones in our RA sample) could have influenced our results; to this regard, GOL, CER and non TNF-inhibitors were associated with a lower prescription rate. Moreover, AHD do not provide detailed information on clinical characteristics, such as disease activity and severity, which could act as confounders over the risk of infections. AHD limitations involve lack of control of data collected for nonclinical purposes and misclassification biases, too; other limitations of AHD-based studies, as well known, are intrinsic in their observational design, in particular the possibility of occurring in a "confounding by indication" bias and the possible presence of unmeasured confounders (38, 39). Results did not change even after adjusting for different calendar periods of bDMARD prescription (data not shown) and this was expected since we suppose the infectious risk of different drugs has not changed over the years. One of the strengths of the RECORD study is its large sample size, which has allowed examining the effects of concomitant bDMARDs and sDMARDs, a common strategy in daily clinical practice that is rarely considered, except for MTX. The use of AHD allows the assessment of complete data without loss at follow-up and the information on drug acquire reflects more truthfully treatment administration.

The results of our study support the use of combination therapy with sD-MARDs without concerns about future safety, while they confirm a potentially harmful effect of corticosteroids on infectious risk. This could support the choice to keep background sDMARD therapy rather than corticosteroids for a better disease control in patients on bDMARDs. ABA emerges as a safer option that could be considered for patients with higher baseline risk of infec-

tion. These findings should ideally be confirmed in large observational studies with complete clinical information.

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