BMC Rheumatology

RESEARCH

Open Access

Real-world evidence of biological treatments in rheumatoid arthritis and spondyloarthritis in Morocco: results of the RBSMR registry

Najlae El Ouardi[1*†], Ihsane Hmamouchi[2,3†], Redouane Abouqal[3], Fadoua Allali[4], Rachid Bahiri[5], Imane El Bouchti[6], Imad Ghozlani[7], Hasna Hassikou[8], Linda Ichchou[9], Saadia Janani[10], Taoufik Harzy[11], Radouane Niamane[12], Ahmed Bezza[1] and Abdellah El Maghraoui[13]

Abstract

Background Regional variability in the effectiveness and safety of biologic therapies for rheumatoid arthritis (RA) and spondyloarthritis (SpA) underscores the need for comprehensive assessment. The aim of this study was to provide real-world evidence of the effectiveness and the safety of biologic for RA, SpA including psoriatic arthritis, in the daily clinical practice.

Materials and methods RBSMR registry was a multicenter, cohort study conducted in 10 university departments of rheumatology. The study included RA and SpA patients receiving biotherapy, either as an initiation or ongoing treatment, and investigated for 3 years. The statistical analysis was performed using JAMOVI software (T student test, Mann–Whitney U test, Chi-squared test, Fisher's exact test, Paired T test and Wilcoxon test).

Results 223 RA and 194 SpA were eligible. After 3 years of follow-up, DAS28 CRP (3.6 ± 1.4 versus 5.8 ± 1.0 at baseline) and ASDAS CRP (1.8[1-2.4] versus 3.5[2.5–4.4] at baseline) significantly improved; 13.8% of RA patients achieved remission based on DAS28 CRP and 20.1% of SpA patients achieved remission based on ASDAS CRP. Overall, 163 and 126 adverse events were reported in RA and SpA patients respectively. Infections were the most frequently reported events with an incidence of 11.8 and 13.4/100 patients-year in RA and SpA respectively. Total incidence rate of tuberculosis was 0.80 patient/100 patients-year.

Conclusions The RBSMR registry provides real-world insights into the effectiveness of biologics in the practice of rheumatology for RA and SpA patients in Morocco. It underscores the critical need for continued vigilance in monitoring and addressing adverse events, with a particular focus on tuberculosis infection.

Keywords Biologic therapy, Registry, Rheumatoid arthritis, Spondyloarthritis, Real world evidence

†Najlae El Ouardi and Ihsane Hmamouchi are contributed equally to this work.

*Correspondence:
Najlae El Ouardi
doc.najlae89@gmail.com

Full list of author information is available at the end of the article

Background

Biological treatments for rheumatoid arthritis (RA) and spondyloarthritis (SpA) have shown significant efficacy and acceptable safety profiles in clinical trials and real-world evidence. However, concerns about toxicity and adverse effects remain, particularly in the context of disease characteristics and comorbidity [1]. The introduction of biologic therapy had significantly improved the outcomes of these chronic inflammatory diseases [2–4]. However, although the therapeutic efficacy and safety of biologic drugs have been demonstrated in multiple studies, 30–40% of patients were found to experience inadequate response either due to a lack of primary response or side effects [4]. Several studies have highlighted the importance of monitoring for infections, infusion reactions, and other potential adverse events in the use of biological drugs for these conditions [5, 6]. Thus, several countries have set up national registries to evaluate the long-term effectiveness and safety of these therapies in clinical practice [2]. Despite advancements in therapy and the implementation of focused management protocols like treat-to-target, not all patients with RA or SpA attain remission or optimal disease control. This evaluation helps gauge the effectiveness of current therapeutic strategies and identifies areas for further enhancement in disease management [7].

Currently, biologic medications such as anti-TNF, rituximab, anti-IL12/23 (ustekinumab) and anti-IL17A (secukinumab) have demonstrated efficacy in SpA and RA through randomized clinical trials and are commercially available in Morocco [8–10]. However, the bDMARDs outcomes in Morocco may be influenced by the higher prevalence of infectious diseases and accessibility to biologics due to social security reimbursement problems [11]. Further evidence is required regarding the effectiveness of these agents in real-world clinical practice settings.

The RBSMR (Registre des Biothérapies de la Société Marocaine de Rhumatologie) is the first national registry designed to comprehensively assess both efficacy and safety of multiple biologic agents in RA and SpA patients with a 3-year prospective follow-up.

The present study was designed to offer real-world evidence regarding the effectiveness and safety of biologic treatments over the 3 years of follow-up utilizing a nationwide drug registry.

Materials and methods

Study design and participants

RBSMR study is a multicentric historical-prospective registry including patients treated for RA or SpA including psoriatic arthritis with biological therapy in the ten rheumatology departments of Moroccan university hospitals.

Initially, 440 patients were enrolled, of whom 419 (225 with RA and 194 with SpA) were subsequently validated for inclusion in the analysis. RA and SpA patients fulfilled ACR/EULAR 2010 criteria and ASAS 2009 criteria respectively. The study included patients aged 18 years and above who were receiving biotherapy for RA or SpA, either as an initiation or ongoing treatment (Additional file 1). Written informed consent was obtained from all participants. Patients who were receiving biotherapy for conditions other than RA or SpA, as well as those with juvenile idiopathic arthritis, were excluded from the study.

Participants were removed from the study if they withdrew their informed consent or privacy form. From May 2017 to January 2019, patients were enrolled in the study, which was followed by a 3-year observational period [12]. During the enrollment visit, retrospective data collection was conducted from hospital medical charts or other clinical documents, starting from the initiation of the earliest biologic treatment. Discontinuation of biologic treatment did not constitute a reason for exiting the study. Efficacy and tolerance data were documented at least every six months, with additional assessments triggered by adverse events or changes in treatment. Patients who discontinued their participation in the study were still included in the analyses if they had accessible clinical outcomes.

Ethical approval of the RBSMR registry study was provided by ethics committee for biomedical research of Mohammed V University of Rabat and the Faculty of medicine and pharmacy of Rabat (approval number: A-RS-308/2017).

Follow up

A standardized follow-up electronic questionnaire collecting tolerance and efficacy of biologic was completed 6 monthly for 3 years (Additional file 2) (The methods have been described in detail elsewhere [12]).

Baseline characteristics and outcome measures

The baseline assessment included socio-demographic data (age, gender, antecedents, comorbidities) and characteristics of RA and SpA (disease duration, ACPA, type of SpA, HLA B27, disease activity and functional scores, concomitant csDMARDs, bDMARDs and glucorticosteroids).

Efficacy of bDMARDs after 3 years of treatment was assessed using different scores: DAS28 for RA, ASDAS CRP and BASDAI for SpA. Remission was defined as DAS28 < 2.6 in RA patients and ASDAS CRP < 1.3 in SpA patients [13, 14]. Good response EULAR was defined in RA patients as DAS28 ≤ 3.2 + decrease of

baseline DAS28 > 1.2 and in SpA patients as BASDAI < 4 + decrease of baseline BASDAI > 2 or > 50% [15, 16].

Safety of biologics was assessed by treatment emergent adverse events (diagnosed with physical examination, laboratory tests, radiologic or immunological parameters) during the 3 years of follow-up.

Statistical analysis

Analyses were carried out using the final database covering the 3-year period of follow-up frozen on April 2022. JAMOVI used for statistical analysis. Homogeneity of the variables was assessed with the Kolmogorov Smirnov test. Continuous variables were expressed as means with standard deviation, while non-continuous variables were reported as medians with interquartile ranges. Categorical variables were presented in absolute and percentages values. The differences in baseline demographic and clinical features between bDMARD naive and bDMARD non naive RA and SpA patients were assessed using T student test (for continuous variables), Mann–Whitney U test (for non-continuous variables) and the Chi-squared test or Fisher's exact test (for categorical variables). To compare activity scores over 3 years of follow-up between bDMARD naive and bDMARD non naive patients, we used T student test and Mann–Whitney U test in RA and SpA patients respectively. To analyze differences between activity scores at the bDMARD initiation and after 3 years of follow-up, we used Paired T test and Wilcoxon test in RA and SpA patients respectively. A p value less than 0.05 was considered significant.

Figures analyzing the current bDMARD and activity scores (DAS28 and ASDAS CRP) in RA and SpA patients over 3 years of follow-up were assessed using STATA and JASP softwares.

Results

Characteristics of patients

During the study, which lasted 3 years, a total of 223 RA and 194 SpA were treated with biological drugs. Overall median age at inclusion in the RBSMR was 53 and 39 years with a median disease duration of 146 and 131 months for RA and SpA respectively. 160 RA and 137 SpA received a first line bDMARDs. At baseline, the most commonly used drug was rituximab in RA patients (59.6%) and etanercept in SpA patients (33%). Patients were prescribed bDMARDs in combination with csDMARDs in 91.9% of patients with RA and 56.3% of patients with SpA (Table 1).

When comparing baseline demographic and clinical features, we found that bDMARD naive SpA patients had a shorter disease duration than bDMARD non naive patients (85 versus 133 months; $p = 0.01$). Baseline activity and functional scores in RA (DAS28 CRP, HAQ) and SpA (BASDAI, ASDAS CRP, BASFI) did not differ significantly between bDMARD naive and bDMARD non naive patients (Table 2).

Over the 3 years of follow up, rituximab and etanercept remained the main commonly used biologic in RA and SpA patients respectively (Fig. 1).

Efficacy assessment

After 3 years of follow-up, we found a statistically significant improvement of activity scores (Fig. 2). A mean DAS28 CRP was 3.6 ± 1.4 versus 5.8 ± 1.0 at baseline and a median ASDAS CRP was 1.8 [1-2.4] versus 3.5 [2.5–4.4] at baseline (Table 3).

bDMARD naive RA patients had significantly higher mean DAS28 CRP than bDMARD non naive patients ($p = 0.008$). No differences were noted at 2 and 3 years of follow-up. There were no differences between bDMARD naive and bDMARD non naive patients when comparing DAS28 ESR and ASDAS CRP in RA and SpA patients respectively (Fig. 3).

Remission was achieved in 13.8% RA based on DAS28 CRP, 8.5% RA based on DAS28 ESR and 20.1% SpA based on ASDAS CRP (Fig. 4). Good response EULAR was registered in 17% RA based on DAS28 CRP, 12.6% RA based on DAS28 ESR and 33% SpA.

Adverse events

Overall, 163 and 126 adverse events were reported in RA and SpA patients respectively (Table 4). The most commonly reported adverse events were infections, mainly nonspecific infections, in both diseases with an incidence rates of 11.8 and 13.4/100 patients-year respectively.

One extra pulmonary tuberculosis in a patient with RA taking etanercept and 8 tuberculosis infections (4 pulmonary and 4 extra pulmonary) in SpA patients taking anti-TNF were reported in our registry. The incidence rates for tuberculosis infection were 0.16 and 1.55 patient/100 patients-year in RA and SpA patients respectively.

During the 3 years of follow up, malignancy was observed in 3 patients with RA taking tocilizumab (1 non-Hodgkin lymphoma, 1 bladder cancer and 1 breast cancer) and in 2 patients with SpA exposed to etanercept (1 vocal cord carcinoma and 1 multiple myeloma). The incidence rates were 0.50 and 0.18 patient/100 patients-year in RA and SpA patients respectively.

In our registry, 30 RA discontinued the biologic therapy due to adverse events: hypersensitivity reaction ($n = 12$), non specific infection ($n = 5$), tuberculosis infection ($n = 1$), viral infection ($n = 1$), cancer ($n = 3$), psoriasis ($n = 1$), Hepatic cholestasis/ cytolysis ($n = 3$), uveitis ($n = 2$) and neutropenia ($n = 2$). The bDMARDs interrupted were rituximab ($n = 15$), tocilizumab ($n = 9$), adalimumab ($n = 3$), infliximab ($n = 2$) and golimumab ($n = 1$). 26 SpA patients experienced adverse events leading to

Table 1 Baseline demographic and clinical features of rheumatoid arthritis (**a**) and spondyloarthritis patients (**b**)

(a)

Variables	**RA patients Value (*N* = 223)**
Age [a] (years) (*N* = 223)	53 [45–59]
Gender [b] (*N* = 223)	
Men	28 (12.6)
Female	195 (87.4)
Disease duration [a] (months) (*N* = 191) Missing: 32	146.0 [97.3-219.1]
Antecedents	
Tuberculosis infection [b] (*N* = 215)	20 (9.3)
Missing [c]	8 (3.5)
Hepatitis infection (*N* = 223)	6 (2.7)
Comorbidities	
Arterial hypertension [b] (*N* = 223)	36 (16.1)
Diabetes [b] (*N* = 223)	46 (20.6)
Dyslipidemia [b] (*N* = 216)	30 (13.9)
Missing [c]	7 (3.1)
Heart disease [b] (*N* = 223)	7 (3.1)
Depression [b] (*N* = 223)	12 (5.4)
Osteoporosis [b] (*N* = 223)	50 (22.4)
Colonic diverticulosis [b] (*N* = 223)	1 (0.4)
Current smoking/ smoking cessation < 1 year [b] (*N* = 223)	4 (1.8)
ACPA positive [b] (*N* = 168)	149 (88.7)
Missing [c]	55 (24.6)
DAS28 CRP (*N* = 175)	
<2.6 [b]	1 (0.6)
2.6≤ ≤ 3.2 [b]	3 (1.7)
3.2< ≤5.1 [b]	50 (28.6)
>5.1 [b]	121 (69.1)
Missing [c]	48 (21.5)
HAQ [a] (*N* = 147) Missing: 76	1.2 [0.5–1.8]
Glucorticosteroids current use [b] (*N* = 223)	210 (94.2)
Concomitant csDMARD [b](*N* = 223)	205 (91.9)
Current bDMARD [b] (*N* = 223)	
Anti-TNF	
Etanercept	18 (8.1)
Infliximab	4 (1.8)
Adalimumab	13 (5.8)
Golimumab	2 (0.9)
Rituximab	133 (59.6)
Tocilizumab	53 (23.8)

[a] Median and interquartile ranges; [b] Number and percentage valid; [c] Number and percentage

RA = rheumatoid arthritis; ACPA = anti citrullinated protein antibodies; DAS28 = Disease Activity Score 28; HAQ = Health Assessment Questionnaire; csDMARD = conventional synthetic disease modifying anti-rheumatic drug; bDMARD = biological disease-modifying anti-rheumatic drug

(b)

Variables	**SpA patients Value (*N* = 194)**
Age [a] (years) (*N* = 194)	39 [28–51]
Gender [b] (*N* = 194)	
Men	123 (63.4)
Female	71 (36.6)

Table 1 (continued)

Disease duration [a] (months) (*N* = 146)	131 [85–182]
Missing: 48	
Antecedents	
Tuberculosis infection [b] (*N* = 189)	13 (6.9)
Missing [c]	5 (2.5)
Hepatitis infection [b] (*N* = 187)	2 (1.1)
Missing [c]	7 (3.6)
Comorbidities [b] (*N* = 194)	
Arterial hypertension	11 (5.7)
Diabetes	10 (5.2)
Dyslipidemia	3 (1.5)
Heart disease	2 (1)
Depression	5 (2.6)
Osteoporosis	22 (11.3)
Current smoking/ smoking cessation < 1 year	21 (10.8)
Type of SpA (*N* = 194)	
Axial SpA [b]	186 (96.4)
Missing [c]	1 (0.5)
Peripheral SpA [b]	7 (3.6)
Missing [c]	1 (0.5)
Uveitis [b] (*N* = 186)	27 (14.5)
Missing [c]	8 (4.1)
Psoriasis [b] (*N* = 188)	13 (6.9)
Missing [c]	6 (3.0)
Inflammatory bowel disease [b](*N* = 187)	20 (10.7)
Missing [c]	7 (3.6)
HLA B27 positive [b] (*N* = 53)	35 (66)
Missing [c]	141 (72.6)
BASDAI [a] (*N* = 159)	5.1[4.0–6.0]
Missing: 35	
BASFI [d] (*N* = 136)	5.3 ± 2.2
Missing: 58	
ASDAS CRP [b] (*N* = 114)	
<1.3	9 (7.9)
1.3≤ <2.1	6 (5.3)
2.1≤ <3.5	41 (36)
≥3.5	58 (50.9)
Missing [c]	80 (41.2)
Concomitant csDMARD [b] (*N* = 190)	107 (56.3)
Missing [c]	4 (2.0)
Current bDMARD [b] (*N* = 194)	
Anti-TNF	
Etanercept	64 (33.0)
Infliximab	49 (25.3)
Adalimumab	59 (30.4)
Golimumab	19 (9.8)
Secukinumab	3 (1.5)

[a] Mean ± ecart type; [b] Number and percentage valide; [c] Number and percentage; [d] Mean ± ecart type

SpA = spondyloarthritis; HLA B27 = human leucocyte antigen B27; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath ankylosing spondylitis functional index; ASDAS = Ankylosing Spondylitis Disease Activity Score; csDMARD = conventional synthetic disease modifying anti-rheumatic drug; bDMARD = biological disease-modifying anti-rheumatic drug

Table 2 Comparison of baseline demographic and clinical features of rheumatoid arthritis (**a**) and spondyloarthritis (**b**) between bDMARDs naive and bDMARDs non naive groups

(a)

Variables	bDMARDs naive Value (*N* = 46)	bDMARDs non naive Value (*N* = 177)	*p*
Age [a] (years)	53 [40–58]	53 [45–60]	0.21
Gender [b]			0.91
Men	6 (13)	22 (12.4)	
Female	40 (87)	155 (87.6)	
Disease duration [a] (months)	121 [63–231]	155 [109–219]	0.27
DAS28 CRP [b]			0.85
<2.6	-	1 (0.8)	
2.6≤ ≤ 3.2	1 (2.3)	2 (1.5)	
3.2< ≤5.1	13 (30.2)	37 (28)	
>5.1	29 (67.4)	92 (69.7)	
HAQ [a]	1.2 [0.5–1.8]	1 [0.5–1.6]	0.66
Glucorticosteroids current use [b]	36 (78.3)	130 (73.4)	0.505
Concomitant csDMARD [b]	43 (93.5)	162 (91.5)	1.0

[a] Median and interquartile ranges; [b] Number and percentage valid

DAS28 = Disease Activity Score 28; HAQ = Health Assessment Questionnaire; csDMARD = conventional synthetic disease modifying anti-rheumatic drug

(b)

Variables	bDMARDs naive Value (*N* = 30)	bDMARDs non naive Value (*N* = 164)	*P*
Age [a] (years)	33 [25–45]	40 [29–52]	0.054
Gender [b]			0.67
Men	18 (60)	105 (64)	
Female	12 (40)	59 (36)	
Disease duration [a] (months)	85 [48–140]	133 [85–191]	0.01
Type of SpA [b]			
Axial SpA	29 (96.7)	157 (96.3)	1
Peripheral SpA	1 (3.3)	6 (3.7)	1
With Uveitis	5 (16.7)	22 (14.1)	0.71
With Psoriasis	2 (6.7)	11 (7.0)	1
With Inflammatory bowel disease	4 (13.3)	16 (10.2)	0.53
BASDAI [a]	5.1 [4.2–5.8]	5.1 [4.0–6.0]	0.83
BASFI [c]	5.2 ± 2.5	5.3 ± 2.1	0.38
ASDAS CRP [b]			0.38
<1.3	-	9 (10.2)	
1.3 ≤ < 2.1	1 (3.8)	5 (5.7)	
2.1≤ <3.5	11 (42.3)	30 (34.1)	
≥3.5	14 (53.8)	44 (50.0)	
Concomitant csDMARD[b]	17 (56.7)	90 (56.3)	0.96

[a] Median and interquartile ranges; [b] Number and percentage valid; [c] Mean ± ecart type

SpA = spondyloarthritis; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath ankylosing spondylitis functional index; ASDAS = Ankylosing Spondylitis Disease Activity Score; csDMARD = conventional synthetic disease modifying anti-rheumatic drug

bDMARD discontinuation: non specific infection ($n = 5$), tuberculosis infection ($n = 8$), viral infection ($n = 2$), cancer ($n = 1$), psoriasis ($n = 2$), uveitis ($n = 4$), hypersensitivity reaction ($n = 2$), inflammatory bowel disease ($n = 1$) and lupus ($n = 1$). The bDMARDs discontinued were infliximab ($n = 10$), adalimumab ($n = 8$), etanercept ($n = 4$), secukinumab ($n = 3$) and golimumab ($n = 1$).

There were 13 registered deaths during the study period (8 RA and 5 SpA patients). The incidence rates were 1.32 and 0.93 patient/100 patients-year in RA and SpA patients respectively. Infections ($n = 7$) and cardiovascular events ($n = 2$) were the most common causes of death. Other documented causes of mortality related to bDMARDs were decompensation of hepatic cirrhosis ($n = 1$) and lymphoma ($n = 1$). Of the fatal infections, 3 were registered as sepsis, 1 as covid-19 infection, 1 as multifocal tuberculosis, 1 as postoperative infection after total knee arthroplasty and 1 as leukocytoclastic vasculitis infection.

Discussion

In the present study, we demonstrated that 8.5–13.8% of RA patients and 20.1% of SpA patients followed in routine clinical care and treated with biologic drugs achieved clinic remission. 31.3–33.9% RA and 23.7% SpA of this study fell into the active disease category according to the various composite scores. Overall, 289 adverse events were recorded in all RA and SpA patients during the period study.

There are several bDMARDs available for the treatment of RA. Of the available choices, rituximab was found to be the most frequently used biological drug in patients with RA in our registry (59.6%). This is easily explained by three main reasons in our Moroccan context: Firstly, rituximab cost nearly half the cost of the other biologics in Morocco. Secondly, it is easier to use especially in patients living in far regions of Morocco (two hospital infusions at a 15 days interval), and thirdly it was considered a priori safer for use regarding tuberculosis risk in a tuberculosis endemic country. In patients with SpA, etanercept was the most used drug in our registry (33%) and this is probably also related to the lower risk of tuberculosis attributed to this drug compared to anti-TNF antibodies. Indeed, several studies have shown that monoclonal anti-TNF have higher tuberculosis infection rates than the soluble TNF receptor and non anti-TNF drugs [17, 18].

Efficacy of bDMARDs was consistent with what is classically reported with improvement of measures of symptomatic activity of the diseases. Although remission was the ultimate purpose of RA and SpA treatment, the definition of remission in clinical practice was unclear. DAS28 based on CRP or ESR and ASDAS CRP have been widely considered the most optimal tools to classify

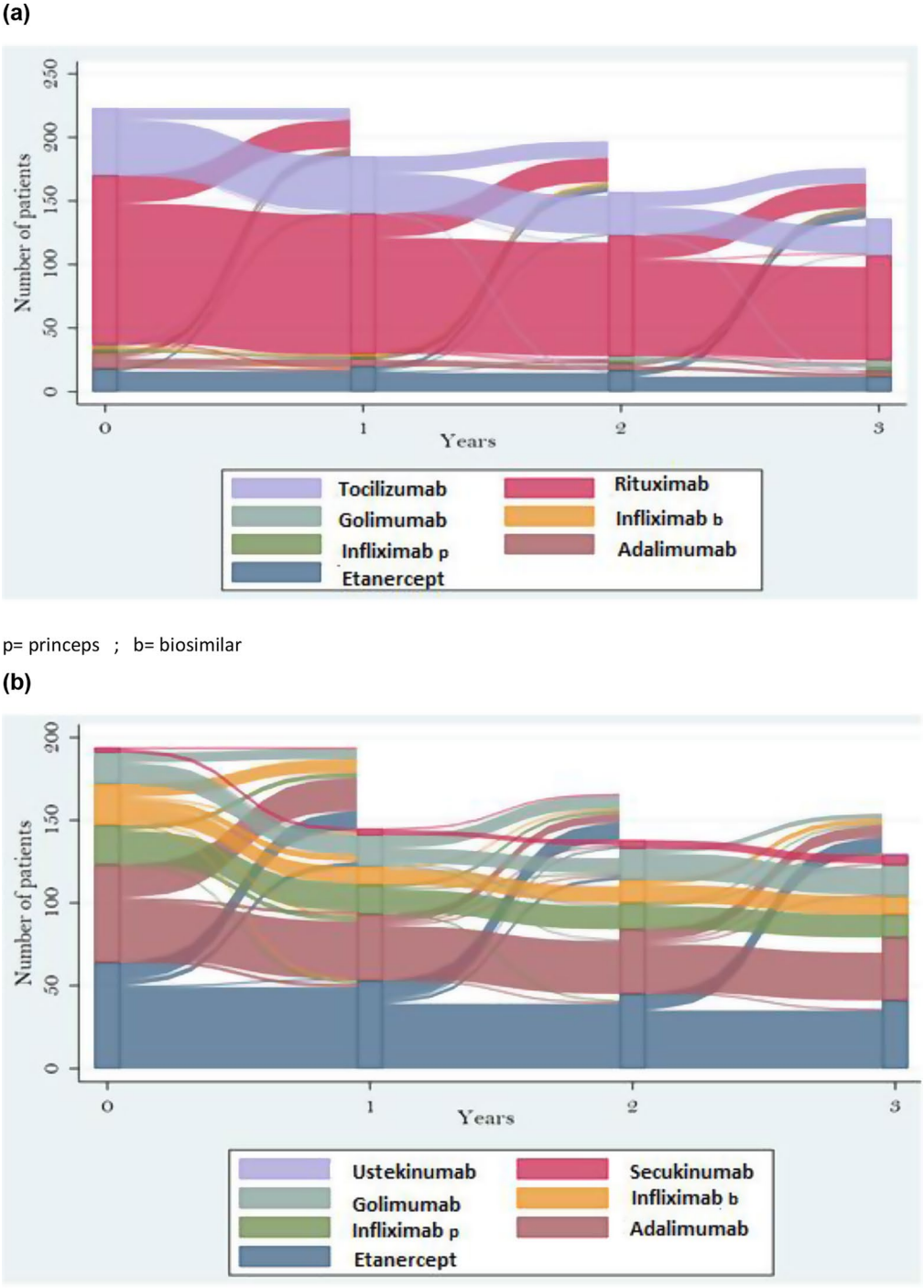

Fig. 1 Current bDMARD in RA (**a**) and SpA (**b**) patients over 3 years of follow-up

disease activity in real-world clinical practice of RA and SpA patients [19, 20]. At year 3, 19 RA achieved remission in response to DAS28 ESR (8.5%). The remission rate was higher when it was based on DAS28 CRP (13.8%).

Higher rates of remission were reported in many real-life data of RA. Reported remission rate to the first bDMARD was observed in 28% RA patients of a four-year real-life tunisian experience [21]. The Korean registry (KOBIO-RA) of RA patients treated with bDMARDs and anti-JAK achieved remission in 45.5% based on DAS28 ESR and 65.9% based on DAS28 CRP [19]. Furthermore, 27.7% RA treated with tocilizumab, as first-line

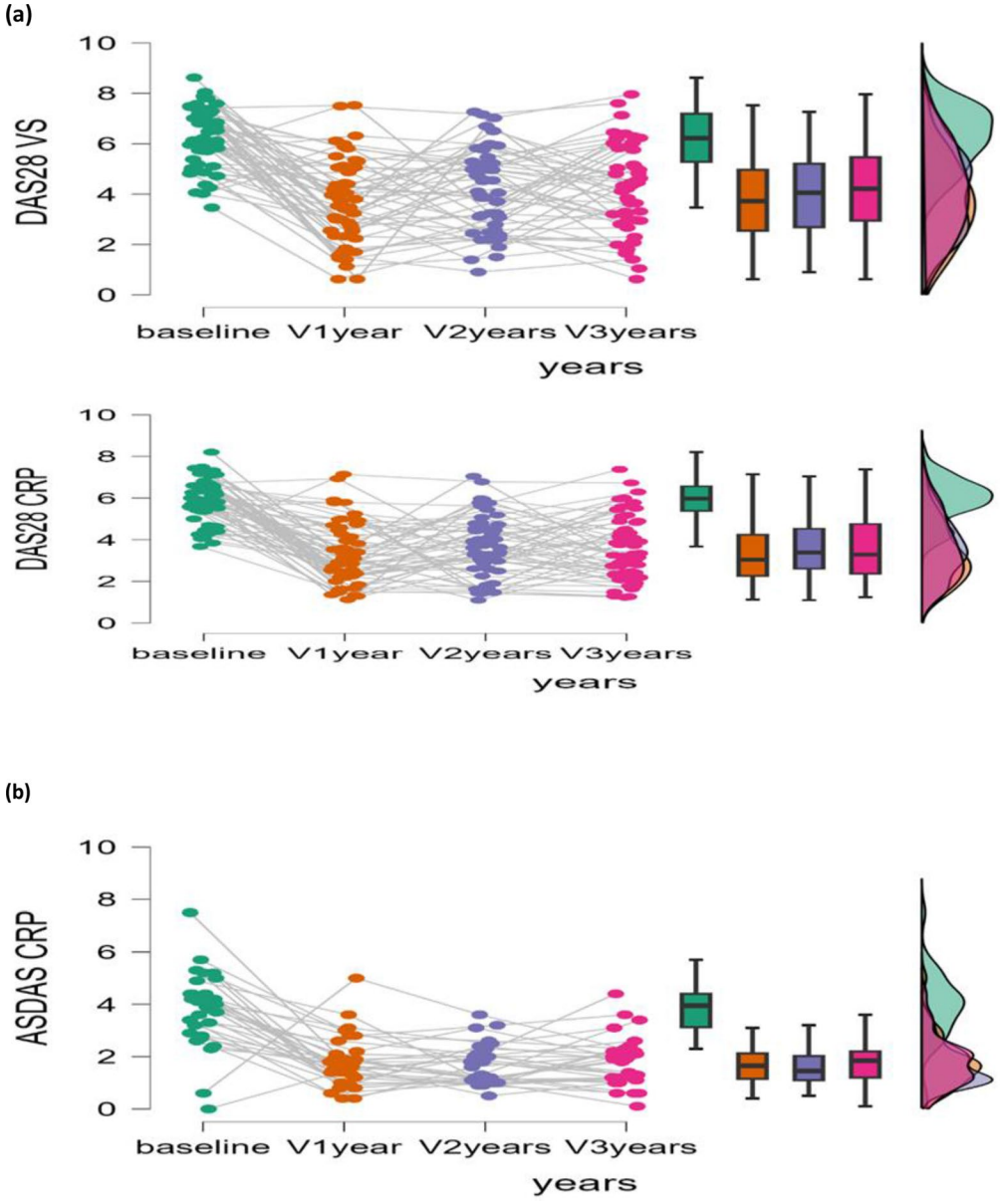

Fig. 2 Activity scores in RA (**a**) and SpA (**b**) patients over 3 years of follow-up

Table 3 Comparison of scores activity in RA and SpA patients during 3 years of follow-up

Scores	At inclusion	At 3 years	*p*
Rheumatoid arthritis			
DAS28 CRP [a]	5.8 ± 1.0	3.6 ± 1.4	< 0.001
DAS28 ESR [a]	6.2 ± 1.1	4.0 ± 1.5	< 0.001
Spondyloarthritis			
BASDAI [b]	5.1 [4.0–6.0]	2.0 [1.2-4.0]	< 0.001
ASDAS CRP [b]	3.5 [2.5–4.4]	1.8 [1.0-2.4]	< 0.001

[a] Mean ± ecart type; [b] Median and interquartile ranges

RA = rheumatoid arthritis; SpA = spondyloarthritis; DAS28 = Disease Activity Score 28; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; ASDAS: Ankylosing Spondylitis Disease Activity Score

biologic treatment, achieved DAS28 ESR remission in the Turkish registry TURKBIO after 2 years of follow-up [22]. Missing data on DAS28, higher disease duration, higher previous biologic exposure and the longer follow-up duration in the Moroccan cohort may explain this difference.

The remission rate in our SpA patients was 20.1%. Similar results were reported in data collected from 13 European registries of axial spondyloarthritis (axSpA) treated with anti-TNF at 12 months (20 to 22%) [23]. The French DESIR cohort reported remission in 17% SpA exposed to anti-TNF at 5-year follow-up [20]. 72.2% axial SpA achieved remission or low disease activity in real world multicenter study from Middle Eastern countries after

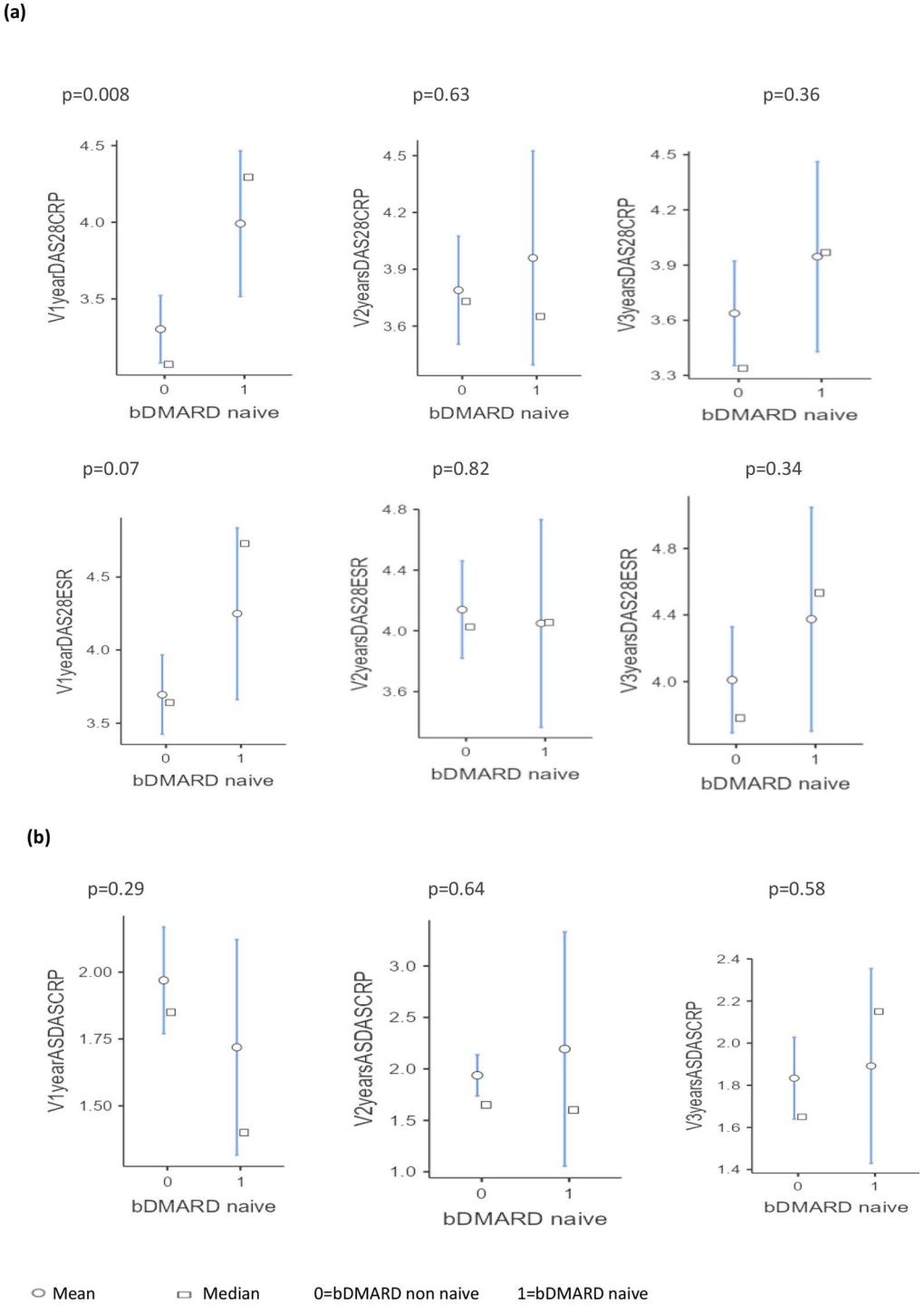

Fig. 3 Comparison of activity scores in RA (**a**) and SpA (**b**) patients over 3 years of follow-up

a 3 month follow-up period. bDMARDs were used in 87.9% SpA [24].

As stated before, chronic rheumatic diseases are associated with an increased prevalence of several comorbidities, such as infection, malignancy, cardiovascular disease, depression and osteoporosis. It is well established that biological therapy may increase the risk of serious infections due to its potent immunosuppressive effects [25]. Safety reports in our study were comparable to other registries with non-specific infections as the main adverse events especially in the first year, even if some divergences may be noted between registries that are related to differences in some patients' characteristics, such as disease activity, previous exposure to

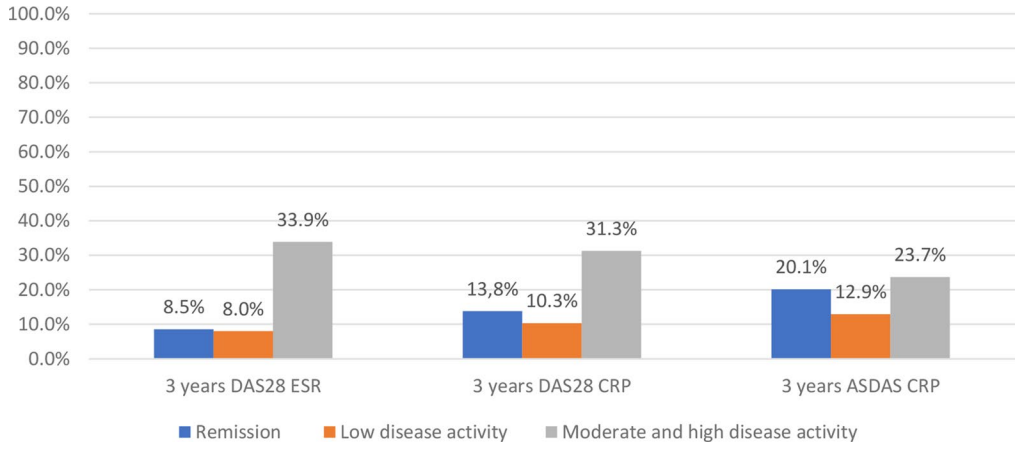

Fig. 4 Disease activity categories in RA and SpA patients at year 3 of follow-up

Table 4 Adverse events of bDMARDs in RA and SpA patients during 3 years of follow up

Variables	**Rheumatoid Arthritis Value (N = 223)**			**Spondyloarthritis Value (N = 194)**		
Adverse events	At 1 year	At 2 years	At 3 years	At 1 year	At 2 years	At 3 years
Infection [a]	19.7	8.51	9.03	29.22	12.46	8.17
Non specific infection	16.5	7.36	6.66	18.18	11.07	4.67
Tuberculosis	-	-	0.53	3.27	0.56	0.59
Atypical mycobacteria	-	0.50	-	-	-	-
Fungal infection	2.4	-	-	2.71	0.56	1.19
Viral infection	-	0.50	1.60	2.15	1.72	1.19
Cancer [a]	0.47	0.50	0.53	-	-	0.59
Solid tumor	-	0.50	0.53	-	-	-
Skin cancer	-	-	-	-	-	-
Lymphoma	0.47	-	-	-	-	-
Other hematological malignancies	-	-	-			0.59
Paradoxical effects [a]	0.95	0.50	1.06	3.83	1.14	4.24
Skin reaction	0.47	-	1.06	0.53	-	0.59
Uveitis	0.47	0.50	-	3.26	1.14	3.01
Sarcoidosis	-	-	-	-	-	-
Vasculitis	-	-	-	-	-	-
Inflammatory bowel disease	-	-	-	-	-	0.59
Auto-immune diseases [a]	0.47	-	-	-	-	0.59
Demyelinating disease	-	-	-	-	-	-
Anti-phospholipid syndrome	-	-	-	-	-	-
Lupus	0.47	-	-	-	-	0.59
Hypersensitivity reaction [a]	2.02	2.03	1.06	3.93	1.13	-
Immediate hypersensitivity reaction	1.00	1.00	1.06	3.93	1.13	-
Delayed hypersensitivity reaction	0.95	1.00	-	-	-	-
Ileocolonic disease [a]	-	-	-	0.53	-	-
Hepatic cholestasis/ cytolysis [a]	2.89	2.02	2.16	1.61	0.56	-
Hematological disorders [a]	9.62	5.71	2.15	1.06	0.56	0.59
Leucopenia	2.39	0.50	1.06	-	-	-
Neutropenia	3.88	4.10	1.06	0.53	-	-
Thrombocytopenia	3.05	1.00	-	0.53	0.56	0.59
Hypercholesterolemia [a]	3.38	4.65	2.16	1.07	1.14	0.59

[a] exposure-adjusted incidence rate (100 patients/year)

biologic drugs, disease duration, comorbidities, age, and concomitant exposure to steroids [26].

Tuberculosis infection has always been given special attention in patients with rheumatic diseases under bDMARDs. It is more likely to be disseminated and extrapulmonary than are other tuberculosis cases. Although analysis of tuberculosis sites revealed a predominance of pulmonary tuberculosis [27, 28]. In our registry, the total incidence rate of tuberculosis was 0.80 patient/100 patients-year (0.16 in RA and 1.55 in SpA). Tuberculosis cases were lower than the reported rates in the South African registry SABIO [29] (1.24/100 person years for biologic users), likely due to the drug choices as mentioned before and the efficacy of applied screening rules and chemoprophylaxis in high-risk patients following the guidelines of the Moroccan Society of Rheumatology [30]. British Society for Rheumatology Biologics registry (BSRBR) found a lower incidence rate (0.095 patient/100 patients-year) in RA cohort treated with anti-TNF during the total follow-up of 34 025 person-years with lower cases after exposure to soluble receptor than monoclonal antibodies [17].

Evaluating the influence of bDMARDs on cancer risk in patients with rheumatic diseases is challenging since these patients have an increased risk of some cancers [31]. The Swedish nationwide cohort study found an incidence rate of 0.97 and 0.91 patient/100-year for a first invasive solid or hematologic malignant neoplasm in RA initiators of anti-TNF as first biologic therapy, and for anti-TNF as second bDMARD respectively [32]. Higher cancer incidence rate was found in SpA patients of GISEA registry [33] during the follow-up period of up to 12 years of treatment with anti-TNF (0.63 patient/100 patients-year) and a collaborative study from the ARTIS and DANBIO registers [34] of SpA patients initiating a first anti-TNF (0.43 patient/100 patients-year). The most frequently reported cancer sites were lung, breast, colorectum, and the female and male reproductive systems. In all studies exploring the malignancy associated with bDMARDs, it is unclear if the effect seen is truly a medication effect or is linked to the disease and the use of other medications such as corticosteroids [35].

In our study, we found an incidence rate of mortality of 1.14 patient/ 100 patients-year (1.32 and 0.93 patient/100 patients-year in RA and SpA respectively) with 3 sepsis recorded. The overall incidence rate of mortality was low in the RBSMR population compared with previous registry studies. Notably, SUNSTONE registry reported a crude mortality rate of 1.66/100 patients-year in RA patients who received ≥ 1 dose of rituximab with a total follow-up of 3844 patients-year [36]. Standardized mortality ratio was 1.56 in psoriatic arthritis patients of the BSRBR during a total follow-up of 5956.5 persons-year [37].

Additionally, published studies have demonstrated that chronic inflammation in RA and SpA increased mortality by accelerating atherosclerosis leading to cardiovascular disease [38]. Investigating the mortality risk in treatment with biologics, CorEvitas RA registry showed that exposure to anti-TNF agents reduced certain causes of mortality risk compared with patients not exposed [39].

Importantly, infections and cardiovascular events as the two leading causes of death in our registry is consistent with reported data of a large five-years observational study of RA treated with rituximab [36]. Furthermore, previous data of a nationwide registry study investigating the underlying causes of death among Norwegian patients with RA, psoriatic arthritis and axSpA found that cardiovascular diseases, neoplasms and respiratory diseases were the major causes of mortality [40].

Our study had some limitations. First, the study sample remains low. Second, the lack of recording of several baseline variables such as characteristics of patients (antecedents, comorbidities), characteristics of RA and SpA diseases (disease duration, type of SpA, activity scores), concomitant csDMARD and lack of radiographic outcomes in some RA and SpA patients may have affected the efficacy assessment. Third, the follow-up period was 3 years and this might be too short to assess the safety of bDMARDs. However, it is important to consider that a registry naturally reflects the patterns of drug utilization in the society in which it is based. It is thus ideally representative of drug utilization patterns within a given country or geographic area. In our case, it was a huge effort to gather all the rheumatology departments of the country to participate and to maintain this effort for nearly five years. We believe that a real-world Morocco-based, robust observational registry will become even more important in the coming years with the proliferation and dissemination of biosimilar agents and new synthetic drugs such as JAK inhibitors. Patients, practitioners, payers, and society in general deserve to see real world local data on the performance of these costly agents.

Conclusions

Our registry showed low remission rates in both RA and SpA patients. It provides real-world insights into the effectiveness of biologics in the practice of rheumatology for RA and SpA patients in Morocco.

Non-specific infections were the main adverse events of our registry with lower incidence rates of tuberculosis than the reported rates in Africa.

Overall, our findings indicate the important role of continued pharmacovigilance and long-term monitoring of patients receiving biologics.

Abbreviations

RA	Rheumatoid arthritis
SpA	Spondyloarthritis
AxSpA	Axial spondyloarthritis
DAS	Disease activity score
ASDAS	Ankylosing Spondylitis Disease Activity Score
ACR	American College of Rheumatology
EULAR	European League Against Rheumatism
ACPA	Anti citrullinated protein antibodies
HLA B27	Human leucocyte antigen B27
ASAS	Assessment in SpondyloArthritis International Society
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
bDMARD	Biologic disease-modifying anti-rheumatic drug
csDMARD	Conventional synthetic disease modifying anti-rheumatic drug
HAQ	Health Assessment Questionnaire
BASFI	Bath Ankylosing Spondylitis Functional Index
CRP	C-reactive protein
ESR	Erythrocyte sedimentation rate
TNF	Tumor necrosis factor
JAK	Janus kinase

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s41927-025-00510-1.

Supplementary Material 1: Electronic questionnaire of the inclusion in the RBSMR

Supplementary Material 2: Electronic questionnaire collecting tolerance and efficacy of bDMARDs every 6 months

Acknowledgements

The authors would like to thank the scientific Committee and national principal investigators of the RBSMR study: Abdellah El Maghraoui, Ahmed Bezza, Lahsen Achemlal, Fadoua Allali, Rachid Bahiri, Redouane Abouqal, Imane El Bouchti, Imad Ghozlani, Taoufik Harzy, Ihsane Hmamouchi, Linda Ichchou, Hasna Hassikou, Saadia Janani, and Redouane Niamane; patients who agreed to participate in this study.

Author contributions

A EM and IH contribute to the design and the conception of the work. N EO analyzed and interpreted the patient data, RA substantively revised the results. N EO, A EM and IH wrote the manuscript. N EO and IH contributed equally to this work. All authors read and approved the submitted manuscript.

Funding

The ancillary study described in this manuscript was done without any type of funding. Data collection was supported by an unrestricted grant from Pfizer, Novartis, Janssen, and Abbvie.

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This project was approved by the ethics committee for biomedical research of Faculty of Medicine, Mohammed V. Rabat. Morocco (approval number: A-RS-308/2017). This study is conducted based on the ethical spirit of the "Declaration of Helsinki". All involved participants provided written informed consent.

Consent for publication

Not applicable.

Competing interests

N EO and RA: None. IH: Support for meeting attendance from Pfizer, Novartis, Sothema. FA: Lecture honoraria from Pfizer, Abbvie, Bottu, Cooper, Sothema, Support for meeting attendance from Pfizer, Janssen, Participation on a Data Safety Monitoring Board or Advisory Board from Sothema, Pfizer, Abbvie. RB: Lecture honoraria from Pfizer, Abbvie, Bottu, Cooper, Sothema, Janssen, Novartis, Hikma, Newbridge, Support for meeting attendance from Pfizer, Janssen, Newbridge, Cooper, Participation on a Data Safety Monitoring Board or Advisory Board from Sothema, Pfizer, Abbvie. EB I: Lecture honoraria from Pfizer, Abbvie, Bottu, Cooper, janssen, novartis, Support for meeting attendance from Pfizer, Janssen, abbvie, hikma, sothema. I EG: Lecture honoraria from Pfizer, Abbvie, Novartis, Sothema, Cooper, Support for meeting attendance from Pfizer, Roche, Participation on a Data Safety Monitoring Board or Advisory Board from Sothema, Pfizer, Janssen, NewBridge Pharmaceuticals. HH: Lecture honoraria from Pfizer, Abbvie, Novartis, Sothema, Cooper, Support for meeting attendance from Pfizer, Roche, Participation on a Data Safety Monitoring Board or Advisory Board from Sothema, Pfizer, Janssen, NewBridge Pharmaceuticals. LI: Lecture honoraria from Pfizer, Bottu, Phi. SJ: None. HT: Lecture honoraria from Abbvie, Bottu, Sothema, Janssen, Support for meeting attendance from Pfizer, Sothema, Participation on a Data Safety Monitoring Board or Advisory Board from Sothema, Pfizer, NewBridge pharmaceuticals, Abbvie, Novartis. RN: Lecture honoraria from Pfizer, Abbvie, Bottu, Jenssen, Sothema, Support for meeting attendance from Pfizer, Janssen, Roche, Participation on a Data Safety Monitoring Board or Advisory Board from Pfizer, Abbvie, Jenssen, Sothema, NewBridge. AB:: Lecture honoraria from Pfizer, Abbvie, Bottu, Cooper, Sothema, Support for meeting attendance from Pfizer, Janssen, Participation on a Data Safety Monitoring Board or Advisory Board from Sothema, Pfizer, Abbvie. A EM: Lecture honoraria from Pfizer, Abbvie, Bottu, Cooper, Sothema, Support for meeting attendance from Pfizer, Janssen, Participation on a Data Safety Monitoring Board or Advisory Board from Sothema, Pfizer, Abbvie.

Author details

[1]Department of Rheumatology, Military Hospital Mohammed V, Ibn Sina University Hospital, Rabat, Morocco
[2]Faculty of Medicine, Health Sciences Research Center (CReSS), International University of Rabat (UIR), Rabat, Morocco
[3]Laboratory of Biostatistical, Clinical and Epidemiological Research, Faculty of Medicine and Pharmacy, Mohammed V University, Rabat, Morocco
[4]Department of Rheumatology B, El Ayachi Hospital, Ibn Sina University Hospital, Salé, Morocco
[5]Department of Rheumatology A, El Ayachi Hospital, Ibn Sina University Hospital, Salé, Morocco
[6]Department of Rheumatology, Arrazi University Hospital, Marrakech, Morocco
[7]Department of Rheumatology, Oued Eddahab Military Hospital, University Ibn Zohr, Agadir, Morocco
[8]Department of Rheumatology, Military Hospital Moulay Ismail, Hassan II University Hospital, Meknes, Morocco
[9]Department of Rheumatology, Mohammed VI University Hospital, Mohammed I University, Oujda, Morocco
[10]Department of Rheumatology, Ibn Rochd University Hospital, Casablanca, Morocco
[11]Department of Rheumatology, Hassan II University Hospital, Fes, Morocco
[12]Department of Rheumatology, Military Hospital Avicenne, Mohammed VI University Hospital, Marrakech, Morocco
[13]Mohammed V University, Rabat, Morocco

Received: 7 August 2024 / Accepted: 5 May 2025
Published online: 27 May 2025

References

1. Virkki L, Aaltonen K, Nordström D. [Biological therapy in rheumatoid arthritis based on ten years of registry surveillance in Finland]. Duodecim. 2010;126:1487–95.
2. Singh JA. Treatment guidelines in rheumatoid arthritis. Rheum Dis Clin North Am. 2022;48:679–89.
3. Tanaka Y. Recent progress in treatments of rheumatoid arthritis: an overview of developments in biologics and small molecules, and remaining unmet needs. Rheumatology (Oxford). 2021;60:VI12–20.
4. Danve A, Deodhar A. Treatment of axial spondyloarthritis: an update. Nat Rev Rheumatol. 2022;18:205–16.

5. da Mota LMH, Cruz BA, Brenol CV, et al. Safe use of biological therapies for the treatment of rheumatoid arthritis and spondyloarthritides. Revista Brasileira De Reumatologia (English Edition). 2015;55:281–309.
6. Cecconi M, Ranza R, Titton DC, et al. Incidence of infectious adverse events in patients with rheumatoid arthritis and spondyloarthritis on biologic Drugs—Data from the Brazilian registry for biologics monitoring. J Clin Rheumatol. 2020;26:73.
7. Lories RJ, De Vlam K. Tumour necrosis factor inhibitors in the treatment of psoriatic arthritis: A view on effectiveness, clinical practice and toxicity. Expert Opin Biol Ther. 2014;14:1825–36.
8. Kavanaugh A, Puig L, Gottlieb AB, et al. Maintenance of clinical efficacy and radiographic benefit through two years of ustekinumab therapy in patients with active psoriatic arthritis: results from a randomized, Placebo-Controlled phase III trial. Arthritis Care Res (Hoboken). 2015;67:1739–49.
9. McInnes IB, Mease PJ, Kirkham B, et al. Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2015;386:1137–46.
10. Colombo D, Frassi M, Pagano Mariano G et al. Real-world evidence of biologic treatments in psoriatic arthritis in Italy: results of the CHRONOS (EffeCtiveness of biologic treatments for psoriatic artHRitis in Italy: an ObservatioNal lOngitudinal Study of real-life clinical practice) observational longitudinal study. *BMC Rheumatol*; 6. Epub ahead of print 1 December 2022. https://doi.org/10.1186/s41927-022-00284-w
11. El Ouardi N, El Maghraoui A, Djossou HJ, et al. Discontinuation of biologic therapy in patients with rheumatoid arthritis and ankylosing spondylitis: analysis from multicenter cohort study. Rheumatol Int. 2023;43:79–87. https://doi.org/10.1007/s00296-022-05237-7.
12. Hmamouchi I, Abouqal R, Achemlal L, et al. The Moroccan registry of biological therapies in rheumatic diseases (RBSMR): methods and preliminaries results. Revue Marocaine De Rhumatologie Rev Mar Rhum. 2019;49:32–7. https://doi.org/10.24398/A.344.2019.
13. Felson DT, Smolen JS, Wells G, et al. American college of rheumatology/european league against rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Ann Rheum Dis. 2011;70:404–13.
14. Machado PM, Landewé R, van der Heijde D. Ankylosing spondylitis disease activity score (ASDAS): 2018 update of the nomenclature for disease activity States. Ann Rheum Dis. 2018;77:1539–40.
15. Fransen J, van Riel PLCM. The disease activity score and the EULAR response criteria. Rheumatic Disease Clin North Am. 2009;35:745–57.
16. Braun J, Pham T, Sieper J et al. *International ASAS consensus statement for the use of anti-tumour necrosis factor agents in patients with ankylosing spondylitis*, www.annrheumdis.com
17. Dixon WG, Hyrich KL, Watson KD, et al. Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British society for rheumatology biologics register (BSRBR). Ann Rheum Dis. 2010;69:522–8.
18. de La Forest Divonne M, Gottenberg JE, Salliot C. Safety of biologic DMARDs in RA patients in real life: A systematic literature review and meta-analyses of biologic registers. Joint Bone Spine. 2017;84:133–40.
19. Koh JH, Lee Y, Kim HA et al. Comparison of remission criteria in patients with rheumatoid arthritis treated with biologic or targeted synthetic disease-modifying anti-rheumatic drugs: results from a nationwide registry. Ther Adv Musculoskelet Dis; 14. Epub ahead of print 2022. https://doi.org/10.1177/17599720X221096363
20. Vegas LP, Sbidian E, Wendling D, et al. Factors associated with remission at 5-year follow-up in recent-onset axial spondyloarthritis: results from the DESIR cohort. Rheumatology (Oxford). 2022;61:1487–95.
21. Boussaid S, Tbini H, Rekik S, et al. Predictors of drug retention and survival rate of bDMARDs in rheumatoid arthritis: A Four-Year Real-Life Tunisian experience. Mediterr J Rheumatol. 2024;35:448–58. https://doi.org/10.31138/mjr.090723.pof.
22. Yazici A, Özdemir Işık Ö, Dalkılıç E et al. A national, multicenter, secondary data use study evaluating efficacy and retention of first-line biologic treatment with tocilizumab in patients with rheumatoid arthritis in real-life setting: results from TURKBIO registry. Sci Rep; 12. Epub ahead of print 1 December 2022. https://doi.org/10.1038/S41598-022-26106-0
23. Nissen M, Delcoigne B, Di Giuseppe D, et al. The impact of a CsDMARD in combination with a TNF inhibitor on drug retention and clinical remission in axial spondyloarthritis. Rheumatology (Oxford). 2022;61:4741–51.
24. Al-Saleh JA, Saab MA, Negm A et al. Predictors of not Achieving Remission or Low Disease Activity in Axial Spondyloarthritis Patients from Middle Eastern Countries: A Prospective, Multicenter, Real-world Study. Oman Med J; 37. Epub ahead of print 1 May 2022. https://doi.org/10.5001/omj.2022.69
25. 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;15:11–34.
26. Lahiri M, Dixon WG. Risk of infection with biologic antirheumatic therapies in patients with rheumatoid arthritis. Best Pract Res Clin Rheumatol. 2015;29:290–305.
27. Fragoulis GE, Dey M, Zhao S et al. Systematic literature review informing the 2022 EULAR recommendations for screening and prophylaxis of chronic and opportunistic infections in adults with autoimmune inflammatory rheumatic diseases. *RMD Open*; 8. Epub ahead of print 2 November 2022. https://doi.org/10.1136/RMDOPEN-2022-002726
28. Iannone F, Cantini F, Lapadula G. Diagnosis of latent tuberculosis and prevention of reactivation in rheumatic patients receiving biologic therapy: international recommendations. J Rheumatol Suppl. 2014;91:41–6.
29. Pettipher C, Benitha R. Tuberculosis in biologic users for rheumatic diseases: results from the South African Biologics Registry (SABIO). *Ann Rheum Dis*; 79. Epub ahead of print 2020. https://doi.org/10.1136/ANNRHEUMDIS-2019-216128
30. Tahiri L, Iraqi G, Bourkadi J, et al. Recommendations of the Moroccan society of rheumatology (SMR) in collaboration with Moroccan pneumophtisiologists for screening and treatment of tuberculosis under biological anti TNF and not anti TNF and under JAK inhibitors during chronic inflammatory rheumatism. Rev Mar Rhum. 2021;58:3–18. https://doi.org/10.24398/A.438.2022.
31. Kremer J, Binghamiii cliftono. Postapproval comparative safety study of Tofacitinib and biological Disease-Modifying antirheumatic drugs: 5-Year results from a united States-Based rheumatoid arthritis registry. ACR Open Rheumatol. 2021;3:173–84.
32. Wadström H, Frisell T, Askling J. Malignant neoplasms in patients with rheumatoid arthritis treated with tumor necrosis factor inhibitors, Tocilizumab, abatacept, or rituximab in clinical practice: A nationwide cohort study from Sweden. JAMA Intern Med. 2017;177:1605–12.
33. Atzeni F, Carletto A, Foti R, et al. Incidence of cancer in patients with spondyloarthritis treated with anti-TNF drugs. Joint Bone Spine. 2018;85:455–9.
34. Hellgren K, Dreyer L, Arkema EV, et al. Cancer risk in patients with spondyloarthritis treated with TNF inhibitors: a collaborative study from the ARTIS and DANBIO registers. Ann Rheum Dis. 2017;76:105–11.
35. Karmacharya P, Shahukhal R, Ogdie A. Risk of malignancy in spondyloarthritis: A systematic review. Rheum Dis Clin North Am. 2020;46:463–511.
36. Winthrop KL, Saag K, Cascino MD, et al. Long-Term safety of rituximab in rheumatoid arthritis: analysis from the SUNSTONE registry. Arthritis Care Res (Hoboken). 2018;71:993–1003.
37. Fagerli KM, Kearsley-Fleet L, Mercer LK, et al. Malignancy and mortality rates in patients with severe psoriatic arthritis requiring tumour-necrosis factor alpha Inhibition: results from the British society for rheumatology biologics register. Rheumatology (Oxford). 2019;58:80–5.
38. Tang CH, Yu F, Huang CY, et al. Potential benefits of biologics on stroke and mortality in patients with rheumatoid arthritis: A nationwide population-based cohort study in Taiwan. Int J Rheum Dis. 2019;22:1544–52.
39. Greenberg JD, Kremer JM, Curtis JR, et al. Tumour necrosis factor antagonist use and associated risk reduction of cardiovascular events among patients with rheumatoid arthritis. Ann Rheum Dis. 2011;70:576–82.
40. Kerola AM, Kazemi A, Rollefstad S, et al. All-cause and cause-specific mortality in rheumatoid arthritis, psoriatic arthritis and axial spondyloarthritis: a nationwide registry study. Rheumatology (Oxford). 2022;61:4656–66.

Publisher's note