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ORIGINAL ARTICLE

Retention rate of a second line with a biologic DMARD after failure of a first-line therapy with abatacept, tocilizumab, or rituximab: results from the Italian GISEA registry

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Abstract

Objectives EULAR recommendations do not suggest which biologic disease-modifying anti-rheumatic drug (bDMARD) should be preferred after failure of a first bDMARD in the treatment of rheumatoid arthritis (RA). In particular, few data are available regarding the effectiveness of a second-line bDMARD after failure of abatacept (ABA), tocilizumab (TCZ), and rituximab (RTX). The aim of this study was to analyze the retention rate of a second line with tumor necrosis factor inhibitors (TNFi) or other mechanisms of action (MoAs), after the failure of either RTX, TCZ, or ABA.

Methods Two hundred and seventy-eight RA patients from the Italian GISEA registry were included in the study. RTX was the first bDMARD in 18% of patients, ABA in 45.7%, and TCZ in 36.3%, while the second bDMARD was a TNFi (group 1) in 129 patients and an agent with a different MoA (group 2) in 149.

Results During a median follow-up of 22 months (IQR 68), 129 patients discontinued their treatment; patients of group 1 discontinued the treatment more frequently than patients of group 2 ($p<0.001$) with retention rates of 33.6±5.7% and 63.6 ±4.6% after 104 weeks for group 1 and group 2, respectively ($p<0.001$). At multivariate analysis, the mechanism of action was the only predictor for the maintenance in therapy.

Conclusions According to our data, ABA, RTX, and TCZ seem to maintain a good retention rate also when used as a second-line therapy, suggesting their use after the failure of a non-TNFi as first-line therapy. However, specifically designed studies are needed to evaluate the more appropriate therapeutic strategies in RA, according to the first-line drug, including new targeted synthetic DMARDs.

Key Points
- *A large proportion of rheumatoid arthritis patients fail the first biologic DMARD.*
- *Few data are available about the efficacy of biologic DMARD after the failure of a non-TNF inhibitor.*
- *Abatacept, rituximab, or tocilizumab seem to maintain a good retention rate after the failure of a first-course therapy with a non-TNF inhibitor.*

Keywords Abatacept · Retention rate · Rheumatoid arthritis · Rituximab · TNF inhibitors · Tocilizumab

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Introduction

Rheumatoid arthritis (RA) is a chronic immune-mediated disease that causes inflammation, pain, and swelling of the joints, typically affecting hands [1]. The advent of biologic disease-modifying anti-rheumatic drugs (bDMARDs) has significantly improved the RA prognosis, often leading to a sustained disease remission [2–4], but randomized controlled trials (RCTs), head to head studies, and meta-analysis have failed to show the superiority of one class of bDMARD or targeted synthetic DMARDs (tsDMARDs) over the others in terms of clinical efficacy and radiographic outcomes [5–8]. Indeed, in spite of the attempts to personalize treatments based upon peculiar patient's characteristics, the most recent EULAR recommendations do not give a hierarchical order in the choice of the first bDMARD or tsDMARD [9]. However, for historical reasons, in clinical practice, tumor necrosis factor inhibitors (TNFi) are commonly the first choice among biologic agents. Nevertheless, about 30–40% of patients do not respond to the first TNFi by showing persistent disease activity and withdrew from therapy [10]. Therefore, which bDMARD should be taken in account after failure of a first biologic drug has been a matter of debate in rheumatology community and the safety and efficacy of biological DMARDs after a non-TNF inhibitor-biological DMARD is one of the points included in the research agenda of the "EULAR Recommendations for the treatment of rheumatoid arthritis."

On the other hand, the therapeutic choices have both significant prognostic and economic implications, since multiple treatment failures have been associated with increased structural joint damage and cost for the health system [11–13].

Mainly, in registry-based studies, after a first-course therapy with TNFi, the retention rate of a second-line TNFi or bDMARDs with a different mechanism of action (MoA) is similar [14]. Hence, according to international recommendations, the selection of a second-course of bDMARD or tsDMARDs is mainly left to the clinician's preference and the rheumatologist should decide whether to choose another TNFi or to switch to a tsDMARDs or to a biologic drug with a different MoA [9], such as interleukin-6 receptor blocking monoclonal antibody tocilizumab (TCZ), the T-cell co-stimulation inhibitor abatacept (ABA), and the anti-CD20 B-cell depleting agent rituximab (RTX). In recent years, ABA, TCZ, and RTX have been proposed as first-line therapy instead of TNFi in clinical practice in many patients when having clinical-biologic characteristics, but no data are available regarding the retention rate of a second-line bDMARD after inadequate response to a first-course therapy with TCZ, ABA, or RTX.

The aim of this study was to compare the effectiveness and drug retention rate of a second-line biologic therapy with TNFi or other MoA, after switching from a first-course treatment with either RTX, TCZ, or ABA in RA patients from the GISEA Italian national registry.

Methods

GISEA registry

The "Gruppo Italiano di Studio sulla Early Arthritis" (Italian Group for the Study of Early Arthritis; GISEA) has developed and maintained a nationwide registry to promote the study of patients with inflammatory arthritis treated with bDMARDs according to standard of care criteria [9, 15]. The registry involves 21 hospital and community-based rheumatology units throughout Italy and enrols patients aged ≥18 who have signed a written consent form upon enrolment. Patients are enrolled when starting a bDMARD and data are recorded at baseline and every 6 months thereafter.

Patients are diagnosed with RA on the basis of the 1987 or 2010 American College of Rheumatology (ACR) criteria [16] and the data collected included age, gender, ethnicity, disease duration, concurrent glucocorticoids, and conventional DMARDs (namely, methotrexate, leflunomide, sulphasalazine, hydroxychloroquine), smoking status, body mass index (BMI), the 28-joint Disease Activity Score (DAS28), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), anti-citrullinated peptide antibodies (ACPA), rheumatoid factor (RF), and side effects. Comorbidities recorded included anemia, anxiety/depression, cardiovascular diseases (coronary artery diseases, chronic heart failure, arrhythmias), arterial hypertension, cerebrovascular diseases, gastropathies, liver diseases, nephropathy, peripheral vasculopathy, diabetes, chronic obstructive pulmonary diseases, and cancer. Extra-articular manifestations of patients' rheumatic disease (rheumatoid nodules, interstitial lung disease, sicca syndrome, and vasculitis) were also collected.

Patient population

Patients were enrolled in the study when a second bDMARD was administered after the failure of a first-line treatment with either ABA, RTX, or TCZ from January 1, 2010, to December 31, 2019. For all patients, demographic, clinical, and serological data, intake of glucocorticoids and conventional synthetic DMARDs (csDMARDs), extra-articular manifestations, and comorbidities were recorded. Moreover, the clinical status was re-evaluated after 52 weeks, with a focus on disease activity and persistence in therapy. When a patient discontinued a bDMARD, the time of discontinuation was also recorded. Time to discontinuation was defined as the time interval between the drug initiation and last administration plus one dispensation interval.

Statistical analysis

Continuous variables were reported as median and interquartile ranges (IQR) and categorical variables as absolute numbers and percentages. The differences between patients who stopped or continued the treatment were analyzed using the Mann-Whitney nonparametric test for continuous variables, while the chi-squared test was used for categorical variables. Univariate and multivariate analyses were performed using logistic Cox regression model. Cox regression analysis was performed to analyze the effect of the baseline features on the drug discontinuation. Retention rate was expressed as estimated median time and 95% confidence interval (95% CI) [17].

The baseline variables considered were gender, disease duration, comorbidities, DAS28, ESR, concurrent use of glucocorticoids and DMARDs, BMI, extra-articular manifestations, and smoking habit. Patients with more than 15% of missing data were excluded from the analysis. Analyses were made using the STATA14 Software (StataCorp LLC, College Station, TX, USA), with a p value ≤0.05 considered to be statistically significant.

The power was estimated in relation to the rate of a second line with TNFi or other MoA, after the failure of either RTX, TCZ, or ABA which represents the primary outcome of the study. Given the characteristics of the patients considered eligible and on the basis of the information derived from the study, the rates in the group were 30.2% and 38.9%. The power calculation is based on the total sample size and effect size (proportion 30.2% and 58.9%), with an alpha of 0.05; estimated power for a two-sample proportions test was 90%. Power and sample size were calculated with the software.

Table 1 Demographic, clinical, and serological features of rheumatoid arthritis patients enrolled in the study

Patients enrolled	278
Females/males (number)	224/54
Age at enrolment (median; IQR)	57 (18)
Disease duration, months (median; IQR)	6 (10)
Current smoker (%)	22.7
ACPA (%)	67.8
Rheumatoid factor (%)	69.8
Comorbidities (%)	55.4
BMI (median; IQR)	24.8 (5.5)
Extra-articular manifestations (%)	15.8
First-line bDMARD (%)	
Rituximab (%)	18.0
Abatacept (%)	45.7
Tocilizumab (%)	36.3
Steroid therapy (%)	63.3
DMARDs (%)	64.7
Methotrexate (%)	50.7
Other DMARDs (%)	21.9
ERS (mmh)	18.5 (24)
C-Reactive protein (mg/L)	1.7 (3.6)
Tender joints 28	5 (8)
Swollen joints 28	3 (6)
DAS28	4.6 (2)

Continuous values are reported as median (interquartile ranges)

Dichotomic values are reported as percentage

ACPA anti-citrullinated peptide antibody, *RF* rheumatoid factor, *DMARDs* disease-modifying anti-rheumatic drugs, *ERS* erythrocyte sedimentation rate, *DAS* disease activity score, *BMI* body mass index

Results

Two hundred and seventy-eight RA patients, who had failed a first non-TNFi bDMARD, were included in the study (females/males 224/54, median age at diagnosis 47 years (IQR 20)). RF and ACPA were positive in 66.7% and 69% of patients, respectively. Comorbidities were reported in 55.4% of patients, mainly cardiovascular diseases (9.6% of patients), arterial hypertension (24.8%), and anxiety/depression (21.6%), while extra-articular RA manifestations were recorded in 15.8%. Median BMI was 24.8 (IQR 5.5). Demographic, clinical, and serologic features are detailed in Table 1.

A combination therapy with a csDMARD was observed in 64.7% of patients, mainly methotrexate (MTX) (50.7%, median dosage 15 (IQR 5) mg weekly), while 63.3% of subjects took low doses of steroids (≤7.5 mg daily of prednisone equivalent).

The prior bDMARD was RTX in 50 patients (18%), ABA in 127 (45.7%), and TCZ in 101 (36.3%) with median retention rates of 15 months (IQR 28), 34 months (IQR 63) for RTX, 14 (IQR 25) for ABA, and 12 (IQR 20) for TCZ, respectively (Fig. 1).

The cause for the first-line therapy discontinuation was primary or secondary loss of efficacy in 12.6% and 54.3% of cases, respectively, adverse events in 18.1%, and other causes (choice of patients, low compliance, etc.) in 15% of patients.

The second bDMARD was a TNFi (group 1) in 129 patients (46.4%) and an agent with a different MoA (group 2) in 149 (53.6%) (see Table 2, Fig. 1). In detail, the TNFi drugs prescribed were etanercept (originator or biosimilar) in 36 patients, infliximab (originator or biosimilar) in 18, adalimumab originator in 39, certolizumab in 27, and golimumab in the latter 9; in group 2, RTX was prescribed in 45 patients, TCZ in 52, and ABA in other 52.

A combination therapy with MTX or other csDMARD was recorded in 70.2% and 67.2% of cases in group 1 and group 2, respectively. The 2 groups showed some differences. Indeed,

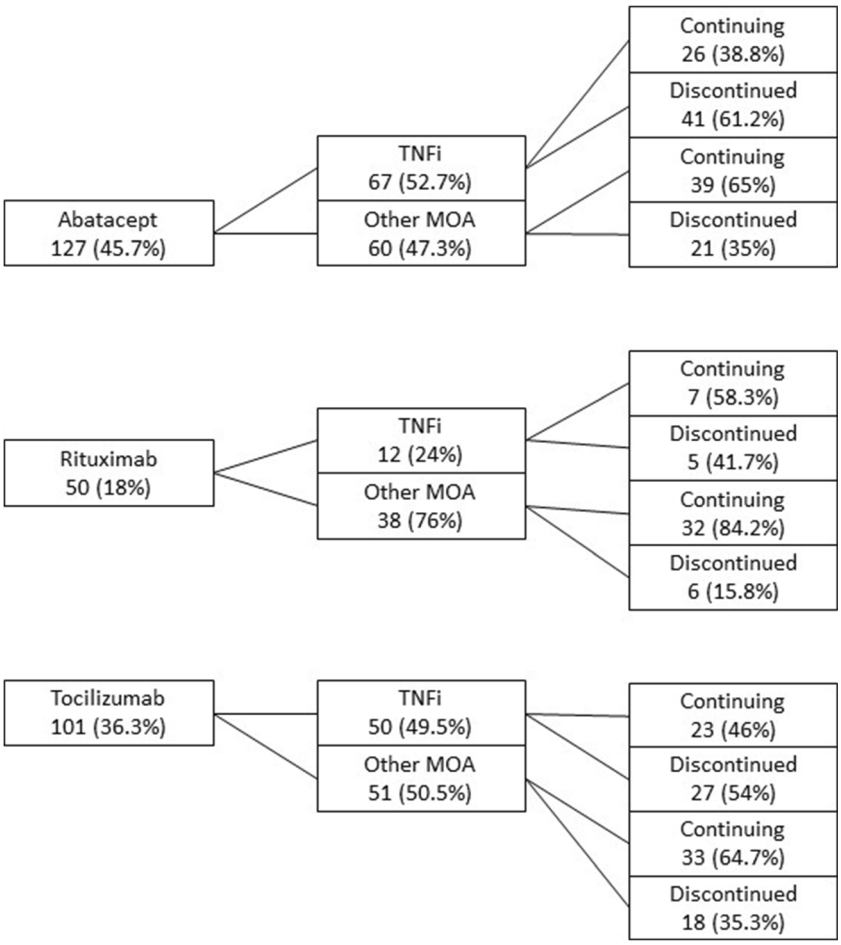

Fig. 1 First-line biological DMARD (abatacept, rituximab, or tocilizumab) and treatment flowchart of patients enrolled in the study

patients of group 1 had a higher prevalence of rheumatoid factor (p=0.01) and ACPA (p >0.05). Patients of group 2 showed a lower number of swollen joints when starting the second bDMARD, but no difference was observed regarding DAS28 score.

During a median follow-up of 22 months (IQR 68), 129 patients discontinued the treatment; in particular, the median follow-up was 21.5 (IQR 68) and 22 months (IQR 70) for group 1 and group 2, respectively. The median time for the discontinuation of the second bDMARD was 9 months (IQR 17) (9 and 10 months for group 1 and group 2, respectively).

Patients of group 1 discontinued the treatment more frequently than patients of group 2 (58.9% vs 30.2%, p<0.001) with an estimated survival time in therapy at Kaplan-Meier test of 70.3 months (95% CI 53.5–87.0) for group 1, and 87.6 months (95% CI 78.1–97.1) for group 2 (p<0.001). Features of patients discontinuing the second bDMARD are reported in Table 3.

The retention rates were 44.6±4.6% and 66.4±4.4% for group 1 and group 2, respectively, after 52 weeks (p<0.001), and 33.6±5.7% and 63.6±4.6% for group 1 and group 2 after 104 weeks (p<0.001, Fig. 2).

In different models including mechanism of action (TNFi or other MoA) and/or DAS28 and/or SJ28 and/or TJ28, the mechanism of action was the only predictor for the maintenance in therapy after 104 weeks (hazard ratio 2.2 for drug discontinuation at 104 weeks, Table 4). The inclusion of baseline values (at time of first bDMARD choice) of ACPA, RF, and other clinical-serological features, such as CRP, did not modify the predictive value of the two models.

According to the first-line bDMARD, patients treated with RTX were shifted to another non-TNFi in 76% of cases (p=0.002), while no differences were recorded for TCZ and ABA. Retention rates were significantly higher in group 2 in patients firstly treated with TCZ and ABA, while no significant difference was recorded for the group firstly treated with RTX.

Discussion

The introduction of bDMARDs has dramatically improved the treatment of RA and has changed the prognosis of this debilitating disease by improving inflammatory signs and

Table 2 Demographic, clinical, and serological features of rheumatoid arthritis patients according to the second-line biologic DMARD

	TNFi	Other MOAs	*p*
Patients enrolled	129	149	
Females/males (number)	106/23	118/31	0.09
Age at enrolment, years (median; IQR)	5.5 (19)	57 (17)	0.81
Disease duration, months (median; IQR)	77 (115)	79 (122)	0.58
Current smoker (%)	15.8	20.9	
ACPA (%)	62.7	72.5	0.06
Rheumatoid factor (%)	63.5	75.2	0.015
Comorbidities (%)	58.1	53	0.33
BMI	25.1 (6.4)	25.8 (6.9)	0.88
Extra-articular manifestations (%)	13.2	18.1	0.43
First-line bDMARD (%)			
Rituximab (%)	9.3	25.5	
Abatacept (%)	51.9	40.3	0.002
Tocilizumab (%)	38.8	34.2	
Steroid therapy (%)	64.3	62.4	0.4
DMARDs (%)	70.2	67.8	
Methotrexate (%)	55.0	47	0.37
Other DMARDs (%)	25.8	18.9	0.51
ERS (mmh)	19 (26)	16 (19)	0.15
C-Reactive protein (mg/L)	2 (4.6)	0.8 (3.5)	0.54
Tender joints 28	5 (11)	5.5 (8)	0.6
Swollen joints 28	4 (7)	2 (6)	0.04
DAS28	4.9 (2.3)	4.3 (2.1)	0.09

Continuous values are reported as median (interquartile ranges)

Dichotomic values are reported as percentage

ACPA anti-citrullinated peptide antibody, *RF* rheumatoid factor, *DMARDs* disease-modifying anti-rheumatic drugs, *ERS* erythrocyte sedimentation rate, *DAS* disease activity score, *BMI* body mass index

symptoms and by allowing the achievement of a sustained remission or at least LDA [18]. Additionally, it has been proven that discontinuation of bDMARDs is associated with a higher risk of losing remission or LDA and with RA radiographic progression [19]. TNFi have been authorized for RA therapy since the 2000s and currently represent the type of bDMARD most commonly used as first-line biologic agents [9, 18]. Presently, the introduction of drugs with different MOAs, routes, and frequency of administration such as TCZ, ABA, RTX, and, more recently, Janus kinase inhibitors (JAKi) has shed light on the possibility of using alternative molecules which could play a pivotal role in blocking the inflammatory cascade and tissue damage [9].

According to the international recommendations, patients with RA who failed to respond to the first course with TNFi therapy should receive either a different TNFi or a second MOA biologic agent, such as ABA, RTX, or TCZ or a tsDMARD, but EULAR never states about the possible second choice after the failure of a non-TNFi drug [9, 20]. Despite the fact that few RCTs have directly compared the efficacy of second-line biologic therapies [21], several studies from registries or indirect meta-analyses have suggested that in patients with TNFi failure, swapping to a biologic with a different MoA could be more effective than switching to another TNFi [14, 22–26]. The scenario is even more ambiguous when the choice falls on a second treatment in RA patients with inadequate response to a first bDMARD other than TNFi. To our knowledge, only an observational retrospective study compared the effectiveness of tocilizumab and TNFi in RA patients after failure of a prior bDMARD. However, this study lacks in giving information on which and how many bDMARDs were previously taken [27].

For the first time, our study aimed to compare retention rates of second-course therapy with TNFi or a biologic with different MoAs, after switching from a first-line treatment with either TCZ, ABA, or RTX. The main finding of the study was that TNFi as second-line therapy were discontinued more

Table 3 Demographic, clinical, and serological features of rheumatoid arthritis patients who continue or discontinue the treatment

	Continuing	Discontinuing	*p*
Patients enrolled	121	157	
Females/males (number)	100/21	124/33	0.44
Age at enrolment, years (median; IQR)	54.1 (19)	57 (17)	0.7
Disease duration, months (median; IQR)	118.8 (115)	79 (107)	0.6
Current smoker (%)	19.5	17.8	
ACPA (%)	67.3	68.1	0.92
Rheumatoid factor (%)	71.6	68.3	0.63
Comorbidities (%)	61.2	51	0.09
BMI	25 (5.3)	24.8 (7.4)	0.49
Extra-articular manifestations (%)	22 (18.2%)	22 (14%)	0.34
First-line bDMARD (%)			
Rituximab (%)	9.9	24.2	
Abatacept (%)	52.1	40.8	0.007
Tocilizumab (%)	38.0	35	
Steroid therapy (%)	67.8	59.9	0.21
DMARDs (%)	70.2	67.8	0.8
Methotrexate (%)	48.8	52.2	0.57
Other DMARDs (%)	19.1	22.3	0.55
ERS (mmh)	16 (21)	18 (22)	0.96
C-Reactive protein (mg/L)	1.6 (3.7)	1 (4.2)	0.26
Tender joints 28	6.5 (10)	5 (7)	0.02
Swollen joints 28	4 (6)	2 (6)	<0.001
DAS28	4.8 (2.1)	4.2 (1.9)	<0.001

Continuous values are reported as median (interquartile ranges)

Dichotomic values are reported as percentage

ACPA anti-citrullinated peptide antibody, *RF* rheumatoid factor, *DMARDs* disease-modifying anti-rheumatic drugs, *ERS* erythrocyte sedimentation rate, *DAS* disease activity score, *BMI* body mass index

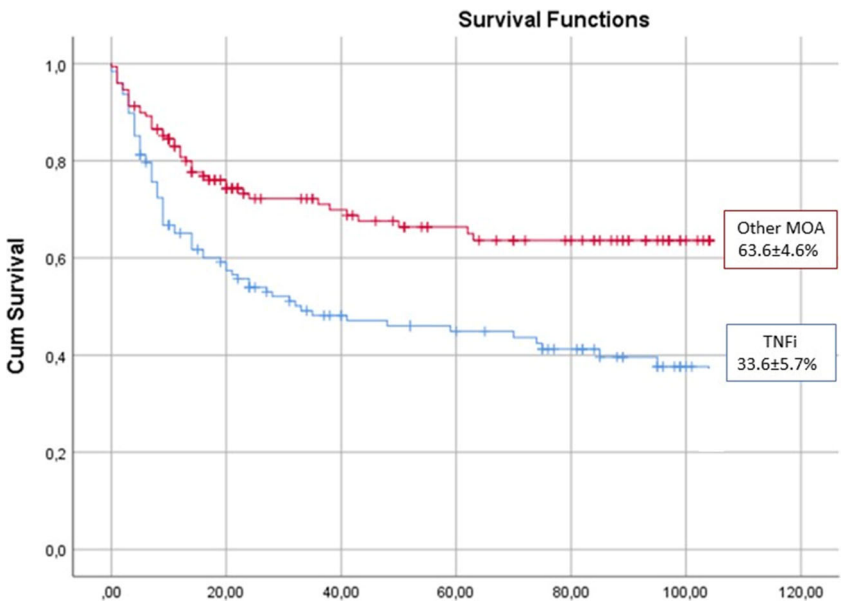

Fig. 2 Retention rates of second-line biological DMARD treatment (TNFi or drugs with other MOA) in rheumatoid arthritis patients, failure to a first course therapy with abatacept, rituximab, or tocilizumab

Table 4 Multivariate analysis. Factors associated to discontinuation of second bDMARD

Parameter	Standard error	Hazard ratio	95% confidence interval	*p*
Model 1				
Mechanism of action (OMOA/TNFi)	0.22	2.18	1.41–3.37	<0.001
DAS28	0.09	1.12	0.94–1.34	0.69
Swollen joints	0.03	1.01	0.96–1.07	0.21
Model 2				
Mechanism of action (OMOA/TNFi)	0.22	2.21	1.43–3.40	<0.001
DAS28	0.11	1.13	0.91–1.40	0.26
Tender joints	0.02	1.00	0.96–1.05	0.87

frequently than ABA, TCZ, and RTX, with an estimated mean survival time in therapy significantly lower for subjects treated with TNFi.

In a retrospective, multicenter study, Vial obtained similar results in 152 patients receiving a second-line bDMARD after RTX failure, recording a higher 1-year retention rate for patients treated with ABA compared with TNFi. However, the aim of the study was to describe the profile of RA patients' failure to a first course with RTX, highlighting the importance of considering patient profile when a therapy is chosen [28]. In a few observational studies, TCZ also has proven to be effective as a second choice in RA patients with insufficient response to RTX [29, 30].

In the clinical settings, there are several factors which may influence therapeutic strategy, even though not always evidence-based supported [31]. In this regard, Monti showed that in a real-life experience, older age and comorbidities are the most important factors in driving the choice towards ABA and TCZ compared with TNFi [32]. In our study, patients treated with ABA, RTX, and TCZ showed more frequently RF and ACPA positivity and this antibody profile may have driven the clinicians' choice towards RTX or abatacept [33, 34]. After the failure of the first bDMARD, the same patient's conditions could have oriented the second treatment choice towards a MOA different from TNFi.

Unlikely, in a real-world setting, the driver for the choice of a non-TNFi drug as first-line therapy is not always recognizable, not allowing to completely exclude a possible selection bias. For example, rituximab is recommended in Italy only as second-line therapy after the failure of a TNFi. Therefore, use of RTX as first-line therapy has to be considered off-label, often reserved to patients with relative contraindications to TNFi.

Also, immunogenicity has been proposed as an important factor when considering the efficacy and retention rate of biologic agents. MTX has been shown to suppress the production of anti-drug antibodies [35, 36], but in the real world, at least 30% of biologic drugs are administered as monotherapy. However, in patients treated with ABA or TCZ, immunogenicity should not be considered a relevant factor, and in our population, the discontinuation of the second bDMARD was not influenced by the association with MTX.

According to the results of our study, as for TNFi, the choice of first bDMARD seems to be crucial, indeed conditioning the response to subsequent lines of therapy; ABA, RTX, and TCZ seem to be able to maintain a good retention rate also when used as second-line therapy, independently from the first-line bDMARD and suggesting their use after the failure of a non-TNFi as first-line therapy.

However, specifically designed studies are needed to evaluate the more appropriate therapeutic strategies, according to the first-line drug, including also the new targeted synthetic DMARDs.

Our work has several limitations, as it is retrospective in design, thus including all bias related to observational registry cohort studies. This approach introduces the selection bias which is the most important limitation of this study. The reason for choosing the non-TNFi as a first-line biologic may have a huge impact on which second biologic treatment you would choose. Nevertheless, this should not influence the retention rate of the second drug.

In conclusion, the identification of conditions associated with the persistence of bDMARDs could help to tailor the therapeutic choice and reduce the frequency of switches from biologic drugs, hence reducing the costs of treatments for national health services and the frequency of flares for patients.

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Author contribution All the authors have contributed significantly to the article, and they agree with the content of the manuscript.

Compliance with ethical standards

Ethics approval The study has been approved by the local ethical committees.

Disclosures None.

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