Tocilizumab and rituximab have similar effectiveness and are both superior to a second tumour necrosis factor inhibitor (TNFi) in rheumatoid arthritis patients who discontinued a first TNFi

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ABSTRACT

Objectives: To compare the effectiveness of a 2nd TNF inhibitor (TNFi), Tocilizumab (TCZ) and Rituximab (RTX), measured by drug retention and by response rates, in rheumatoid arthritis (RA) patients after discontinuing a first-line TNFi and to clarify the reasons and predictors for discontinuation of a second-line biologic.
Material and Methods: Non-interventional prospective study of RA patients exposed to a 2nd TNFi, TCZ or RTX after previous TNFi discontinuation using real-world data from Reuma.pt database. Drug retention was estimated using Kaplan-Meier analysis and Cox models. Crude and LUNDEX adjusted response rates were evaluated at 6 months, 1 and 2 years, and reasons for discontinuation were compared according to biologic class.
Results: In total, 643 patients were included, 88.8% females, with a mean age of 59.4±12.8 years. Of those, 390 (60.7%) initiating a 2nd TNFi, 147 (22.9%) received TCZ and 106 (16.5%) RTX. Drug retention was significantly greater among patients who initiated TCZ (76.4±4.3 months) or RTX (80.8±4.8 months), compared with those who initiated a 2nd TNFi (52.7±2.6 months) (log rank test, p<0.001). In the adjusted Cox model, hazards (HR) of discontinuation were significantly lower for TCZ (HR 0.39, 95% CI 0.23-0.64, p<0.001) and RTX (HR 0.42, 95% CI 0.25-0.72, p=0.001). Smokers had a significantly higher risk for discontinuation (HR 2.43, 95%CI 1.50-3.95, p<0.001) as well as patients with higher Health Assessment Questionnaire (HAQ) at baseline (HR 1.51, 95%CI 1.14-2.00, p=0.004). The proportion of patients in remission or low disease activity according to Clinical Disease Activity Index (CDAI) at 6 months, 1 and 2 years was, respectively, 46.5%/50.0%/61.2% for TNFi, 52.9%/53.6%/69.2% for TCZ and 37.7%/48.0%/ /50.0% for RTX. After LUNDEX adjustment, response rates were, respectively, 33.0%/31.0%/31.8% for 2nd TNFi, 42.8%/41.8%/53.3% for TCZ and 32.0%/39.4%/ /39.0% for RTX. The main reasons for discontinuation were inefficacy for 2nd TNFi and RTX and adverse events for TCZ (p<0.001).
Conclusions: Our findings showed a significantly higher drug retention for TCZ and RTX, compared with 2nd TNFi, and similar persistence among TCZ and RTX, in patients who discontinued a first-line TNFi. These data corroborate the notion that switching to a biologic with a different mode of action is more effective than to a second TNFi.

Keywords: Rheumatoid arthritis; Drug survival; Tumour necrosis factor inhibitors; Tocilizumab; Rituximab.

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INTRODUCTION

The treatment of rheumatoid arthritis (RA) has greatly advanced since the development of biological disease-modifying antirheumatic drugs (bDMARDs), improving symptoms and halting progression of joint damage, with a good safety profile[1].

Tumour necrosis factor inhibitors (TNFi) are highly effective treatments for active RA. However, up to 40%

of patients either fail to respond adequately to TNFi (primary inefficacy) or lose responsiveness over time (secondary inefficacy)[2]. According to Portuguese recommendations[3], the options available to patients with an inadequate response to a first-line TNFi include treatment with a second TNFi or switching to a biological therapy with a different target such as Tocilizumab (TCZ), a monoclonal antibody targeting the interleukin-6 receptor; Rituximab (RTX), an anti-CD20 B-cell-depleting therapy; or abatacept (ABT), a selective co-stimulation modulator[4]. Data about the comparative effectiveness of different switching strategies are, however, limited. After a 1st TNFi failure, a 2nd line TNFi appears to be more likely to fail earlier than a non-TNFi[5–9]. In the absence of head-to-head trials, the effectiveness of different strategies has been studied in routine clinical practice in observational trials at 6 or 12 months. There are a few observational studies comparing the short-term effectiveness of a subsequent TNFi *versus* non-TNFi[1,4,10–16], but long-term data is missing. TNFi are the most commonly used 1st line biologic treatment after conventional DMARDs failure and may well remain so, due to the introduction of biosimilars and their impact on global costs.

The aim of this study was to compare the effectiveness of a 2nd TNFi, TCZ and RTX as measured by retention rates and treatment response rates at 6 months, 1 and 2 years, in RA patients registered at Reuma.pt who previously discontinued their 1st TNFi. The frequency and reasons for treatment discontinuation after switching to a 2nd line biologic (2nd TNFi, TCZ or RTX) were compared and identified predictors of discontinuation.

Reuma.pt (www.reuma.pt), the Rheumatic Diseases Portuguese Register, became active in 2008 and includes patients with varied rheumatic diseases. It provides an excellent source of real-world data and may contribute to fulfil the lack of long-term comparative data among treatment strategies after 1st TNFi failure. The prescription of biological therapies reflects sequential regulatory approvals and national practices and in Portugal TNFi, TCZ and RTX are the therapies most frequently used in RA, unlike others such as ABT. Thus, ABT was not included due to its limited use in Portugal.

MATERIAL AND METHODS

STUDY DESIGN AND POPULATION

Non-interventional study of RA patients exposed to a 2nd TNFi, TCZ or RTX, prospectively followed at Reuma.pt database. Inclusion criteria were: a diagnosis of RA according to the rheumatologist, age ≥ 18 years old, having failed a first-line TNFi and starting a 2nd biologic agent between 2009 and 2018 (date from which the 3 therapeutic classes became available in Portugal) and having baseline demographic and clinical information and follow--up data that could be used to assess treatment effectiveness.

DATA COLLECTION

Demographic data, disease characteristics, concomitant treatments and comorbidities were assessed at baseline (start date of 2nd biologic).

Disease activity (tender joint count [TJC28], swollen joint count [SJC28], patients global/pain visual analogue scale [VAS], physician VAS, erythrocyte sedimentation rate [ESR], C-reactive protein [CPR], Disease activity score-28 joints [DAS28] ESR 4 variables, Clinical disease activity index [CDAI], Simplified disease activity index [SDAI]) and function (Health assessment questionnaire [HAQ]) were collected at baseline and at follow-up, at 6 and 12 months and every year thereafter.

The discontinuation date and reasons for discontinuation were also collected.

After missing data collection, clinical data and disease activity data were subsequently completed by each center.

DEFINITIONS

Seropositivity was considered when rheumatoid factor (RF) and/or anti-citrullinated protein antibodies (ACPA) were positive.

Drug retention was defined as the time until treatment discontinuation defined as: end of treatment registered by the physician, occurrence of any switch to another biological agent (switch); 90-day continuous gap of treatment without a posterior biological treatment, except for RTX; RTX was considered as stopped at either the date of registration of suspension and the date of initiation of a new bDMARD; the timing of administration and the date of suspension were confirmed by a rheumatologist.

Temporary discontinuations corresponding to a <90 days of discontinuation, regardless of the cause, after which the patient restarted the same biological agent, were considered as continuous use of the drug.

Response to biologics was measured by composite disease activity/ response indices, CDAI, SDAI, DAS28

4 variables and European League Against Rheumatism (EULAR) response criteria[17].

Remission was defined as a DAS28 <2.6, a CDAI ≤2.8 and a SDAI ≤3.3. Low disease activity included patients with a DAS28 <3.2, a CDAI ≤10 and a SDAI ≤11[17].

Ineffectiveness included both lack and loss of effectiveness (primary and secondary) according to the rheumatologist opinion.

STATISTICAL ANALYSIS

Baseline population characteristics were compared among the three different biologic classes, using chi-square test and Fisher exact test, as appropriate, for categorical variables or ANOVA test, for equal and unequal variances, for continuous variables.

Drug retention rates of TNFi, TCZ and RTX were estimated using Kaplan-Meier analysis, from initiation of each therapy until discontinuation, switch or last follow-up visit.

Univariate analyses were done with the independent variables age, sex, disease characteristics (disease duration, seropositivity, extra-articular manifestations), comorbidities and baseline disease activity. To obtain a predictor model of discontinuation, we used a Cox model. All the variables considered clinically relevant (age, gender, seropositivity) and all the variables with p-value <0.20 from the univariate analysis were considered for the model and selected by stepwise selection method[18].

Reasons for discontinuing therapy were evaluated using descriptive statistics.

Disease activity at baseline and follow-up was compared according to biologic class using the chi-square or ANOVA test, as appropriate. Follow-up categories were defined as follows: 6 months, 1 year, 2 years, 3 years, 4 years and 5 years. LUNDEX adjustment, in which the fraction of responders is multiplied by the fraction of patients remaining in the study, was used to account for the fraction of patients discontinuing the treatment[19].

All analyses were performed with SPSS v23 and significance level was set at 0.05.

This study was conducted according to the Declaration of Helsinky and the International Guidelines for Ethical Review of Epidemiological Studies. The study protocol was approved by the Coordinator and Scientific Board of Reuma.pt and by the Ethics Committee of the Unidade Local de Saúde do Alto Minho.

RESULTS

A total of 643 patients with the diagnosis of RA who discontinued a 1st TNFi (supplementary Table I) were included, with a mean disease duration until the use of the 1st biologic of 10.1 ± 8.5 years. The main reason for discontinuation of the 1st TNFi was ineffectiveness of therapy (74.1%). After 1st TNFi discontinuation, 390 (60.7%) patients initiated a 2nd TNFi, 147 (22.9%) TCZ and 106 (16.5%) RTX. Considering the 2nd TNFi, 182 patients (46.7%) initiated etanercept, 119 (30.5%) adalimumab, 51 (13.1%) golimumab, 30 (7.7%) infliximab and 8 (2.2%) certolizumab.

The baseline characteristics of the study population at the time of the 2nd biologic prescription are detailed in Table I. At baseline, there were no significant differences in patient and disease characteristics among the 3 treatment groups, except for extra-articular manifestations (more common in the RTX group), education and current full-time employment (both lower in RTX patients). Besides that, discontinuation of the 1st TNFi due to ineffectiveness was superior in the TCZ group compared to the other two groups.

At the beginning of the 2nd biological therapy, the mean age of this population was 59.4 ± 12.8 years and mean disease duration was 13.4 ± 8.8 years. The majority (69.0%) of patients were treated with concomitant methotrexate, but this association was more frequent in the TNFi group (74.1% *vs* 59.0% and 64.2% in TCZ and RTX groups, respectively, p=0.002).

Table II summarizes disease activity according to DAS28, CDAI and SDAI and their components.

DRUG RETENTION

Drug retention according to Kaplan-Meier survival curve was significantly greater (log rank test, p<0.001) among patients who initiated TCZ or RTX, compared with those who initiated a 2nd TNFi (Figure 1). The overall mean drug retention was 64.5±2.2 (min: 0.0; max:120.0) months. Mean retention for 2nd TNFi was 52.7±2.6 (min: 0.0; max: 114.5) months, for TCZ 76.4±4.3 (min: 0.0; max: 106.8) months and for RTX treatment 80.8±4.8 (min: 0.0; max:120.0) months.

Overall treatment retentions rates at 6 months, 1, 2, 3, 4 and 5 years of follow-up were 75%, 69%, 62%, 55%, 51% and 38%, respectively. After 6 months of starting a 2nd TNFi, 71% of patients were maintained on treatment and this percentage decreased to 62% at 1 year, 52% at 2 years, 46% at 3 years, 41% at 4 years and 29% at 5 years of therapy. For the TCZ treatment, 81%

TABLE I. PATIENT AND DISEASE CHARACTERISTICS AT BASELINE

	All patients n=643	TNFi n=390	Tocilizumab n=147	Rituximab n=106	P value
Age (years)	59.4 ± 12.8	59.2 ± 12.9	57.2 ± 11.8	63.5 ± 12.9	NS
Gender (Female)	571/643 (88.8%)	349/390 (89.5%)	128/147 (87.1%)	94/106 (88.7%)	NS
Race (White European origin)	487/514 (94.7%)	287/303 (94.7%)	114/121 (94.2%)	86/90 (95.6%)	NS
Marital status (Married)	195/266 (73.3%)	108/142 (76.1%)	55/83 (66.3%)	32/41 (78.0%)	NS
Education (1st cycle)	187/466 (40.1%)	105/276 (38.0%)	43/107 (40.2%)	39/83 (47.0%)	NS
Current labour situation (Full-time)	173/498 (34.7%)	109/300 (36.3%)	50/115 (43.5%)	14/83 (16.9%)	<0.001
Smoking status (Never smoked)	386/ 524 (73.7%)	240/321 (74.8%)	79/114 (69.3%)	67/89 (75.3%)	NS
Alcohol consumption (Occasional/never consumed)	430/497 (86.5%)	263/305 (86.2%)	97/108 (89.8%)	70/84 (83.3%)	NS
Age at disease diagnosis (years)	43.3 ± 13.3	43.4 ± 13.7	41.8 ± 12.3	44.9 ± 13.4	NS
Disease duration until 1st biologic initiation (Years)	10.1 ± 8.5	9.8 ± 8.6	10.4 ± 8.1	10.8 ± 8.8	NS
BMI (Kg/m2)	27.0 ± 5.1	27.1 ± 5.2	26.4 ± 4.6	27.23 ± 5.0	NS
Rheumatoid factor (yes)	429/570 (75.3%)	251/342 (73.4%)	98/127 (77.2%)	80/101 (79.2%)	NS
ACPA (yes)	359/491 (73.1%)	197/283 (69.6%)	93/116 (80.2%)	69/92 (75.0%)	NS
Erosive disease (yes)	341/456 (74.8%)	199/276 (72.1%)	76/101 (75.2%)	66/79 (83.5%)	NS
Extra-articular manifestations (yes)	163/643 (25.3%)	96/390 (24.6%)	29/147 (19.7%)	38/106 (35.8%)	0.013
DMARD association (yes)	498/632 (78.8%)	318/382 (83.2%)	102/144 (70.8%)	78/106 (73.6%)	0.003
Hydroxychloroquine association (yes)	70/632 (11.1%)	37/382 (9.7%)	16/144 (11.1%)	17/106 (16.0%)	NS
Leflunomide association (yes)	47/632 (7.4%)	29/382 (7.6%)	7/144 (4.9%)	11/106 (10.4%)	NS
Methotrexate association (yes)	436/632 (69.0%)	283/382 (74.1%)	85/144 (59.0%)	68/106 (64.2%)	0.002
Sulfasalazine association (yes)	86/632 (13.6%)	50/382 (13.1%)	24/144 (16.7%)	12/106 (11.3%)	NS
Sjogren's syndrome (yes)	57/547 (10.4%)	33/333 (9.9%)	9/117 (7.7%)	15/97 (15.5%)	NS
Comorbidities (yes)	218/547 (39.9%)	130/333 (39.0%)	46/117 (39.3%)	42/97 (43.3%)	NS
Hypertension (yes)	175/547 (32.0%)	103/333 (30.9%)	34/1117 (29.1%)	38/97 (39.2%)	NS
Hypercholesterolaemia (yes)	51/547 (9.3%)	34/333 (10.2%)	7/117 (6.0%)	10/97 (10.3%)	NS
Diabetes mellitus (yes)	44/547 (8.0%)	26/333 (7.8%)	8/117 (6.8%)	10/97 (10.3%)	NS
Cardiovascular disorder (yes)	54/547 (9.9%)	37/333 (11.1%)	11/117 (9.4%)	6/97 (6.2%)	NS
Discontinuation of the 1st TNFi due to ineffectiveness (yes)	470/634 (74.1%)	294/384 (76.6%)	123/145 (84.8%)	53/105 (50.5%)	<0.001

NS: not significant; BMI: Body Mass Index; ACPA: Anti-citrullinated protein antibodies; DMARD: disease-modifying antirheumatic drugs; TNFi: tumour necrosis factor inhibitor

remained on therapy at 6 months and, at 1, 2, 3, 4 and 5 years, the percentages of patients on treatment were 78%, 77%, 73%, 70% and 64%, respectively. In the RTX group 85% of patients were maintained on therapy after 6 months and, at 1, 2, 3, 4 and 5 years, the rates of persistency decreased to 82%, 78%, 72%, 67% and 50%, respectively.

REASONS FOR DRUG DISCONTINUATION

From the initial 643 patients, 297 (46.2%) discontinued their second biologic therapy during the follow--up. The proportion of patients discontinuing therapy when treated with a 2nd TNFi, TCZ or RTX were 56.4% (220/390), 25.2% (37/147) and 37.7% (40/106), respectively (p<0.001).

The main reason for discontinuation was ineffectiveness for the TNFi and RTX groups, but in the TCZ group adverse events were the main indication for stopping therapy (Table III).

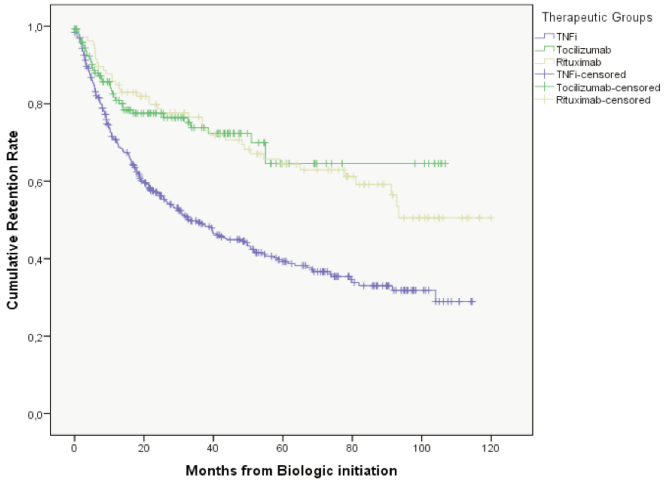
PREDICTORS OF DRUG DISCONTINUATION

When performed the multivariate analysis, treatment with TCZ or RTX decreased the risk of treatment discontinuation, compared to a 2nd TNFi (Hazard Ratio

TABLE II. DISEASE ACTIVITY AT BASELINE

	All patients n=643	TNFi n=390	Tocilizumab n=147	Rituximab n=106	P value
Tender joints 28	9.2 ± 7.4	9.1 ± 7.3	8.9 ± 7.3	10.3 ± 7.9	NS
Swollen joints 28	6.7 ± 5.6	6.0 ± 5.3	7.9 ± 6.1	7.5 ± 5.6	0.01
ESR (mm/ 1st hr)	39.9 ± 27.8	36.8 ± 27.1	44.5 ± 28.4	44.0 ± 27.9	NS
CRP (mg/dl)	2.0 ± 3.0	1.8 ± 2.5	2.3 ± 3.4	2.5 ± 3.7	NS
Patient VAS	59.4 ± 24.4	58.6 ± 24.2	61.0 ± 26.8	59.6 ± 22.0	NS
Pain VAS	58.9 ± 25.2	57.7 ± 24.4	60.7 ± 26.6	60.3 ± 25.7	NS
Physician VAS	48.9 ± 22.4	46.4 ± 21.5	51.6 ± 24.3	53.2 ± 21.6	NS
DAS 28	5.4 ± 1.4	5.3 ± 1.4	5.5 ± 1.5	5.6 ± 1.3	NS
DAS 28 >5.1	273/452 (60.4%)	151/257 (58.8%)	68/111 (61.3%)	54/84 (64.3%)	NS
CDAI	26.5 ± 14.0	25.5 ± 13.4	27.8 ± 15.4	27.8 ± 13.6	NS
CDAI >22	227/401 (56.6%)	123/229 (53.3%)	62/107 (57.9%)	42/65 (64.6%)	NS
SDAI	28.8 ± 15.1	27.8 ± 14.3	29.9 ± 16.8	30.5 ± 14.6	NS
SDAI >26	187/363 (51.5%)	100/208 (48.1%)	52/98 (53.1%)	35/57 (61.4%)	NS
HAQ	1.5 ± 0.1	1.3 ± 0.7	1.5 ± 0.7	1.8 ± 0.6	NS

NS: not significant; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; VAS: Visual Analog Scale; DAS28: disease activity score 28; CDAI: Clinical Disease Activity Index; SDAI: Simple Disease Activity Index.



Months	0	6	12	24	36	48	60	72	84	96	108	120
TNFi	390	316	256	184	138	111	81	61	40	20	6	0
TCZ	147	119	101	74	53	31	19	12	9	9	0	0
RTX	106	99	89	73	66	58	47	41	26	16	6	1

FIGURE 1. Drug retention by months for each group therapeutic; n of patients at risk by months.
TNFi: tumour necrosis factor inhibitor; TCZ: tocilizumab; RTX: rituximab

[HR] 0.39, 95% CI 0.23 to 0.64, p<0.001 for TCZ and HR 0.42, 95% CI 0.25 to 0.72, p=0.001 for RTX). Smoking was associated with a 2.4-fold increased risk of biologic discontinuation (HR 2.43, 95% CI 1.50 to 3.95, p<0.001). In addition, each unit of increase in HAQ at baseline, raised the risk of discontinuation by 51% (HR 1.51, 95% CI 1.14 to 2.00, p=0.004).

TABLE III. REASON FOR DISCONTINUATION OF THE 2ND BIOLOGIC THERAPY

	All patients n=643	TNFi n=390	Tocilizumab n=147	Rituximab n=106	P value
Discontinuation of the 2nd biologic	297/643 (46.2%)	220/390 (56.4%)	37/147 (25.2%)	40/106 (37.7%)	<0.001
Adverse event	75/290 (25.9%)	49/217 (22.6%)	19/35 (54.3%)	7/38 (18.4%)	
Ineffectiveness	165/290 (56.9%)	137/217 (63.1%)	11/35 (31.4%)	17/38 (44.7%)	<0.001
Other reason*	50/290 (17.2%)	31/217 (14.3%)	5/35 (14.3%)	14/38 (36.8%)	

*Neoplasia, pregnancy, non-compliance, refusal of treatment or remission

TABLE IV. PROPORTION OF PATIENTS IN REMISSION OR LOW DISEASE ACTIVITY ACCORDING TO DAS28, CDAI AND SDAI BY TREATMENT GROUP, WITHOUT LUNDEX ADJUSTMENT

	All patients n=534	TNFi n=316	Tocilizumab n=119	Rituximab n=99	P value
At 6 months					
CDAI ≤ 10	143/308 (46.4%)	86/185 (46.5%)	37/70 (52.9%)	20/53 (37.7%)	NS
DAS 28 < 3.2	114/339 (33.6%)	60/203 (29.6%)	42/70 (60.0%)	12/66 (18.2%)	<0.001
SDAI ≤ 11	131/287 (45.6%)	78/176 (44.3%)	36/63 (57.1%)	17/48 (35.4%)	NS
At 1 year					
CDAI ≤ 10	138/273 (50.5%)	77/154 (50.0%)	37/69 (53.6%)	24/50 (48.0%)	NS
DAS 28 < 3.2	111/281 (39.6%)	57/159 (36.1%)	30/63 (47.6%)	10/59 (16.9%)	<0.001
SDAI ≤ 11	117/241 (48.5%)	67/138 (48.6%)	28/57 (49.1%)	22/46 (47.8%)	NS
At 2 years					
CDAI ≤ 10	110/182 (60.4%)	63/103 (61.2%)	27/39 (69.2%)	20/40 (50.0%)	NS
DAS 28 < 3.2	85/191 (44.5%)	43/103 (41.7%)	29/44 (65.9%)	13/44 (29.5%)	0.002
SDAI ≤ 11	100/164 (61.0%)	56/90 (62.2%)	25/36 (69.4%)	19/38 (50.0%)	NS

NS: not significant; DAS28: disease activity score 28; CDAI: Clinical Disease Activity Index; SDAI: Simple Disease Activity Index.

RESPONSE TO TREATMENT

After 6 months, 1 year and 2 years of starting a 2nd biologic treatment, the proportion of patients in remission or low disease activity according to CDAI and SDAI was similar, but according to DAS28 it was significantly higher in the TCZ group (Table IV). However, after LUNDEX adjustment the proportions were lower in TNFi group. Proportion of patients in remission or low disease activity according to CDAI with LUNDEX adjustment at 6 months, 1 and 2 years were fulfilled by 33.0%, 31.0%, 31.8% of patients with a 2nd TNFi, 42.8%, 41.8%, 53.3% with TCZ and 32.0%, 39.4%, 39.0% with RTX, respectively (p>0.05 at 6 months and 1 year; p=0,019 at 2 years). Proportion of patients in remission or low disease activity according to CDAI, crude and LUNDEX adjusted, are presented in Figure 2. At 6 months, 1 and 2 years, DAS28 remission or low disease activity with LUNDEX adjustment were fulfilled by 21.0%, 22.4%, 21.7% of patients with a 2nd TNFi, 48.6%, 37.1%, 50.7% with TCZ and 15.5%, 13.9%, 23.0% with RTX, respectively (p<0.001 at 6 months and 2 years; p=0,002 at 1 year). DAS28 was significantly higher for TCZ at 6 months, comparing with a 2nd TNFi or RTX (2.6±1.8 *vs* 1.3±1.6 for TNFi and 1.2±1.1 for RTX, p<0.001). On the other hand, at 1 and 2 years the DAS28 was similar between the three treatment groups.

Regarding the EULAR response after LUNDEX adjustment, patients who started TCZ were the treatment group with a higher percentage of patients with an EULAR good response. At 6 months, 41.9% of patients treated with TCZ had an EULAR good response, com-

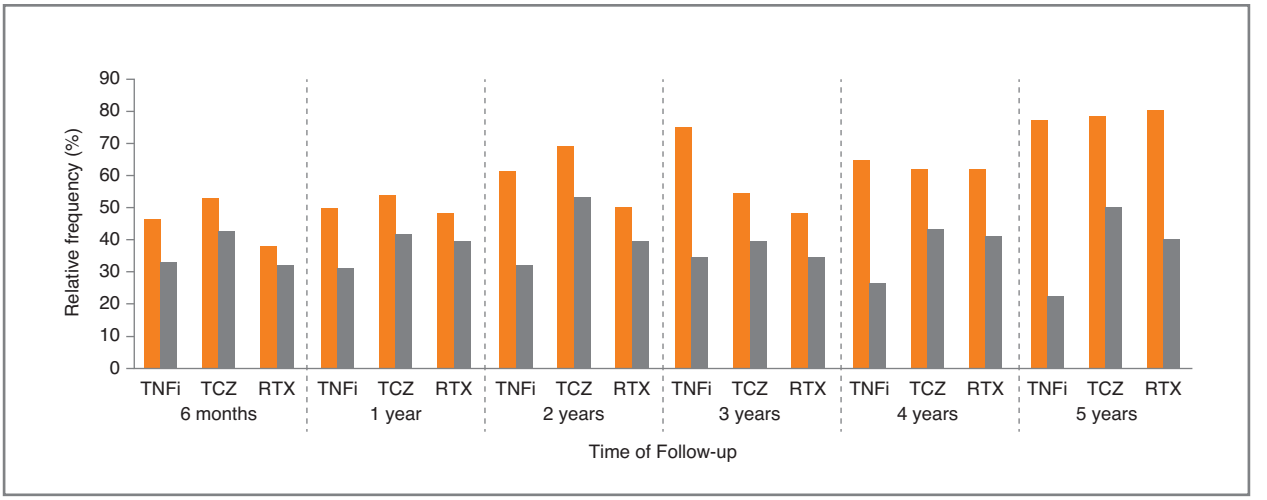


FIGURE 2. Proportion of patients in remission or low disease activity according CDAI (CDAI ≤10) at 6 months, 1 year, 2, 3, 4 and 5 years, in TNFi group, TCZ group and RTX group (p>0.05 at 6 months, 1 and 3 years; p=0.019 at 2 years; p=0.004 at 5 years). Crude - orange bars; LUNDEX adjustment – gray bars.

paring with 16.8% in TNFi group and 23.4% in RTX group (p<0.001). At 1 year, the percentage was 42.5% for TCZ, 17.4% for TNFi and 18.9% for RTX (p<0.001). Two years after treatment initiation, the proportions of patients with an EULAR good response were 43.0% for TCZ, 16.3% for TNFi and 20.0% for RTX (p=0.001).

In the evaluation of the specific components of the disease activity indices (supplementary Table II), TJC was lower for TCZ group at 6 months (2.5±3.4 *vs* 4.8±5.8 for TNFi and 5.6±5.9 for RTX, p<0.001) and at 1 year (2.9±4.1 *vs* 4.3±5.8 for TNFi and 4.7±4.9 for RTX, p=0.043). The SJC, patient global VAS and physician VAS were similar among the three treatment groups at 6 months, 1 year and 2 years.

The CRP was lower in patients treated with TCZ 1 year after therapy initiation, 0.4±1.3 comparing with 1.1±1.9 in TNFi and 1.5±3.5 in RTX (p=0.004). In opposition, there were no statistically significant differences for CRP at 6 months and 2 years of treatment between the three treatment groups. Also the ESR was lower for TCZ group at 6 months (15.2±18.5 *vs* 30.7±24.0 for TNFi and 37.6±26.5 for RTX, p<0.001), at 1 year (11.1±14.7 *vs* 30.7±22.6 for TNFi and 28.8±21.1 for RTX, p<0.001) and at 2 years (10.4±14.1 *vs* 28.1±19.8 for TNFi and 25.9±19.7 for RTX, p<0.001).
In terms of function, there were no statistically significant differences for ΔHAQ at 6 months, at 1 year and 2 years among the three treatment groups (supplementary Table II).

DISCUSSION

Our work shows that after discontinuing a first-line TNFi, drug retention in RA patients is higher if a biologic with a different mode of action (MOA) is started. The aim of RA treatment is to achieve sustained remission or low disease activity, avoiding joint damage, and maintaining function and quality of life. To achieve this objective in real-life, both drug effectiveness and safety are required, which translates in better retention rates. The comprehension of the behaviour of biological therapies after a 1st TNFi discontinuation can help guide clinicians in their decisions about RA treatment. In RA patients registered at Reuma.pt who discontinued a 1st TNFi, mostly due to ineffectiveness, persistence on TCZ and RTX was similar when used as second-line biologic, and superior for both drugs comparing to a 2nd TNF**i**. Although the discontinuation of the 1st TNFi was more frequently associated with ineffectiveness in the TCZ group, potentially associated with a worse response to a 2nd biologic, the retention was higher for these patients.

These results are in line with other studies, indicating greater persistence on a non-TNFi[2,10,13,14,20–22] even though in our population the 2nd TNFi retention rate was higher than previously reported[7]. Also, the persistence on RTX as a 2nd line therapy was slightly higher in our population than reported by Oldroyd *et al.*[23]. This may well be due to the order off appearance of the drugs in the Portuguese market and their reimburse-

ment as well as some difference in local hospital policies.

Most studies evaluating cycling or swapping strategies have been focused on the comparison between a 2nd TFNi and RTX, all demonstrating a superiority of the latter at 6 or 12 months [2,13,14,16,20]. Another two observational studies expanded the analysis to ABT and TCZ, comparing TNFi with the non-TNFi as a group[21,22]. A retrospective analysis with the aim to compare the 5-year retention rate in patients treated with a 2nd TNFi or a non-TNFi showed a significantly higher treatment retention in the non-TNFi group (HR=2.258, p=0.005) even after stratification according to the reason for the 1st TNFi discontinuation[21]. In a 52-week open-label trial, RA patients were randomly assigned to receive a non-TNFi (including TCZ, RTX and ABT) or a TNFi and the therapeutic maintenance rate was significantly higher at weeks 24 and 52 in the non-TNFi group[22].

Despite the elevated percentage of patients failing the 1st TNFi, there is no data from clinical trials on the efficacy of switching to another TNFi, RTX or TCZ when faced with failure of a TNFi.

To our best knowledge, our study is the first one comparing three different MOA as second line biologic therapy for RA. Also, the overall time of exposure is considerably longer than in previous reports[1,2,4,10–16,20,22,24–27].

The main reason for discontinuation was ineffectiveness for the TNFi and RTX groups which is consistent with previous reports[5,7,23]. In TCZ group, adverse events were the main indication for stopping therapy. However, when evaluated the proportion of patients who discontinued their treatment due to adverse events in the overall group, the results were similar between TCZ and TNFi group. In general, the discontinuation rates associated to adverse events were higher than those described in other studies, probably because this is a long-term study thus more likely to capture adverse events compared with short-term data[4,14].

The proportion of patients in remission or low disease activity according to CDAI was similar among the different therapeutic groups, however, after correction for attrition bias, the remission rates were lower with a 2nd TNFi. As expected, given the mechanism of action, TCZ was associated with lower levels of CRP and ESR, which also contributes to better performances of this drug when evaluating indices that include the analytical parameters. A better clinical response with TCZ, when compared with a 2nd TNFi, is consistent with other studies[4,10,21,22]. A Bayesian network meta-analysis involving 1796 patients found that TCZ was the second-line non-TNF biologic with the highest performance regarding an early good response at 6 months based on ACR20 response and acceptable safety profile, followed by RTX, ABT and tofacitinib, and also that none of these options was associated with a significant risk of withdrawal due to adverse events[4]. Also at 52 weeks, a study revealed an higher proportion of patients achieving a good/ moderate EULAR response for non-TNFi (TCZ, RTX and ABT), specifically 69% *vs* 52% for TNFi[22].

The studies comparing short-term effectiveness (6 and 12 months) after a TNFi have suggested that the response rates of a 2nd TNFi are lower than RTX and earlier initiation of RTX may lead to tighter control of the disease activity and improve outcomes[1,2,12–16,20]. This difference was particularly evident among RF positive patients who discontinued their initial TNFi because of inefficacy[2]. Also, a predictive biomarker for the response to RTX may be the positivity to ACPA[28]. In our study, only tobacco and a higher HAQ at baseline showed to be predictors of treatment discontinuation.

RTX remains well tolerated over multiple courses, without significant safety risks or increased rates of adverse events with prolonged exposure[29,30]. The long-term effectiveness of RTX may be superior to the short time data, related with the known delay of the mechanism of action[26].

This study has been conducted in a real-life cohort of bDMARDs users, with the intrinsic limitations of its observational and non-interventional design. In the absence of randomization, patients with a different discontinuation risk may have been directed to a specific biologic, producing selection bias and potentially affecting the analysis. In order to minimize these potential biases, the data analysis was limited to the period from 2009 when all three biologic therapies were available in Portugal. In addition, in most of the cases it was not recorded whether patients had experienced primary or secondary failure of their 1st TNFi and this could be an influencing factor on the biological class chosen and the treatment response.

This study has also some strengths. In addition to be conducted in a real-life setting, the analysis included a high number of patients with a long follow up. Besides that, the comparative analysis was performed between the 2nd TNFi and two non-TNFi separately, allowing to evaluate each of the non-TNFi classes and not only the non-TNFi as a group.

CONCLUSIONS

In summary, the present study corroborates the notion that switching to a biologic with a different mode of action is the best option after failing a TNFi. In terms of disease control, TCZ and RTX performed similarly and both were superior to a 2nd TNFi and with higher retention rates, when used as second-line biologics in RA patients.

The results from this work contribute to clarify the outcome of switching, increasing the possibility of a good response to the 2nd line treatment and thus improving assertiveness in the treatment of refractory patients.

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SUPPLEMENTARY TABLE I. DISTRIBUTION OF 1ST TNFI BY DRUG

	Etanercept	Infliximab	Adalimumab	Golimumab	Certolizumab
n (%)	262/643 (40.7%)	179/643 (27.8%)	134/643 (20.8%)	63/643 (9.8%)	5/643 (0.8%)

SUPPLEMENTARY TABLE II. SPECIFIC COMPONENTS OF DISEASE ACTIVITY INDICES AND FUNCTION AT FOLLOW-UP BY TREATMENT GROUP

	All patients	TNFi	Tocilizumab	Rituximab	P value
At 6 months N=534*					
TJC28	4.4±5.5	4.8±5.8	2.5±3.4	5.6±5.9	<0.001
SJC28	2.9±3.8	2.8±3.7	2.6±3.9	3.6±3.9	NS
VAS	43.4±25.2	42.0±26.3	42.6±23.4	48.8±23.1	NS
CRP	1.3±2.8	1.3±3.1	0.8±1.8	2.1±2.6	NS
HAQ	1.3±0.7	1.2±0.7	1.1±0.7	1.6±0.7	NS
ΔHAQ	0.3±0.6	0.2±0.6	0.4±0.6	0.3±0.5	NS
At 1 year N=447**					
TJC28	4.0±5.3	4.3±5.8	2.9±4.1	4.7±4.9	0.043
SJC28	2.5±3.6	2.5±3.8	2.3±3.6	3.7±3.0	NS
VAS	43.6±25.1	42.4±25.9	46.1±24.3	44.5±23.9	NS
CRP	1.1±2.2	1.1±1.9	0.4±1.3	1.5±3.5	0.004
HAQ	1.2±0.7	1.1±0.6	1.3±0.8	1.5±0.7	0.005
ΔHAQ	0.3±0.6	0.2±0.6	0.5±0.8	0.3±0.5	NS
At 2 years N=332***					
TJC28	4.0±4.7	3.0±5.1	2.3±3.6	4.1±4.5	NS
SJC28	1.8±3.0	1.4±2.3	2.1±3.5	2.7±3.7	NS
VAS	40.4±23.5	39.3±24.4	40.4±23.6	42.9±22.6	NS
CRP	0.98±2.0	1.2±2.2	0.5±1.9	1.1±1.4	NS
HAQ	1.1±0.7	0.9±0.7	1.1±0.7	1.3±0.8	NS
ΔHAQ	0.3±0.7	0.3±0.6	0.5±0.8	0.3±0.6	NS

NS: not significant; TJC28: tender joint count; SJC28: swollen joint count; VAS: patient global visual analogue scale; CRP: C-reactive protein; HAQ: Health assessment questionnaire. *TNFi: n=316; TCZ: n=119, RTX: n=99; ** TNFi: n=257; TCZ: n=101, RTX: n=89; *** TNFi: n=185; TCZ: n=74, RTX: n=73