

# Tocilizumab as a first line biologic agent in rheumatoid arthritis patients with inadequate response to disease-modifying anti-rheumatic drugs: real life experience from the TReasure Registry

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## Abstract Objective

To evaluate the retention rate, treatment response and safety of tocilizumab (TCZ) as first-line biologic treatment in rheumatoid arthritis (RA) patients with inadequate response to disease-modifying anti-rheumatic drugs (DMARD-IR).

## Methods

The TReasure Registry is a multicentre, web-based registry of RA and spondyloarthritis patients across Turkey. DMARD-IR RA patients who received TCZ as first-line biologic treatment were included in this registry for efficacy and safety. Demographic and clinical data, treatments, and adverse events were collected. Drug retention rate was estimated using Kaplan-Meier analysis.

## Results

Among 642 RA patients who ever used TCZ, 258 DMARD-IR RA patients (male/female: 18.2%/81.8%, mean age, 54.41 years) received TCZ as first-line biologic. The median disease duration was 97 (range, 60–179) months and the median TCZ treatment duration was 15 (range, 6–28) months. At the 6<sup>th</sup> and 12<sup>th</sup> months of TCZ treatment, the decrease in disease activity scores from baseline was significant. The Kaplan-Meier analysis revealed the retention rate of TCZ at the 12<sup>th</sup>, 24<sup>th</sup>, 36<sup>th</sup>, and 60<sup>th</sup> months as 81.1%, 73.8%, 66.2%, and 63.6%, respectively. Fifty-seven (22%) patients discontinued TCZ; the main reason being primary or secondary inefficacy (n=29).

## Conclusion

Over 80% drug retention rate at 12<sup>th</sup> month of TCZ treatment in this real-world study was concordant with previously conducted TCZ clinical studies. Significant reductions not only in the disease activity score-28 but also in the simplified disease activity index (SDAI) and clinical disease activity index (CDAI) scores, along with health assessment questionnaire (HAQ) scores, supported the impact of TCZ in RA management with a good safety profile.

## Key words

tocilizumab, biological drugs, rheumatoid arthritis, drug retention, real life data

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## Introduction

With the innovations that have taken place in the last two decades in the treatment of rheumatoid arthritis (RA), the main goals for RA are to decrease joint inflammation and pain, preserve the ability of patients to function in activities of daily life and work, and prevent joint deformity and destruction. The optimal treatment regimen consists of a combined approach that includes both pharmacologic and non-pharmacologic therapies. Since complete recovery from RA is not possible, clinical remission is considered a good outcome (1, 2).

Early treatment with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), such as methotrexate (MTX), has become the standard of care as several studies have suggested that it can slow down disease progression, and potentially induce clinical remission (3). If the patient fails to respond adequately to MTX, the current standard approach is to add other synthetic or biological disease-modifying anti-rheumatic drugs (bDMARDs) to the treatment regimen. Options of bDMARDs generally include tumour necrosis factor inhibitor (TNFi) and non-TNFi agents (CD80/86 costimulation inhibitors, anti-CD20 agents, and anti-interleukin (IL)-6 receptor monoclonal antibodies (4). Although the therapeutic efficacy and safety of TNFi have been proven in a number of studies, it is known that 30–40% of patients develop an inadequate response, either due to a lack of primary response or adverse events (5). Moreover, most TNFi require concomitant MTX for maximum clinical efficacy, whereas tocilizumab (TCZ) has similar efficacy either when used in combination with MTX or as monotherapy (6).

IL-6 is a protein that stimulates B cells to produce antibodies and shows its biological activities by binding only to IL-6 receptor (7, 8). TCZ is a humanised monoclonal antibody against the IL-6 receptor alpha subunit (9). Extensive clinical studies have demonstrated the short and long-term efficacy and safety of TCZ in patients with early-stage and established RA. TCZ (as monotherapy or in combination with csDMARDs) has also shown rapid and sustained im-

provements in clinical and radiographic outcomes and health-related quality of life in real-life studies (10).

TReasure is an ongoing, national, observational database which collects real life data of RA and spondyloarthritis (SpA) patients on bDMARDs or targeted synthetic disease-modifying anti-rheumatic drugs (tsDMARDs) in Turkey (11). The current study aimed to evaluate the retention rate, treatment response and safety of TCZ (monotherapy or in combination with csDMARDs) as first line biologic treatment in RA patients with inadequate response to disease-modifying anti-rheumatic drugs (DMARD-IR) as well as the clinical characteristics of RA patients registered in the TReasure database.

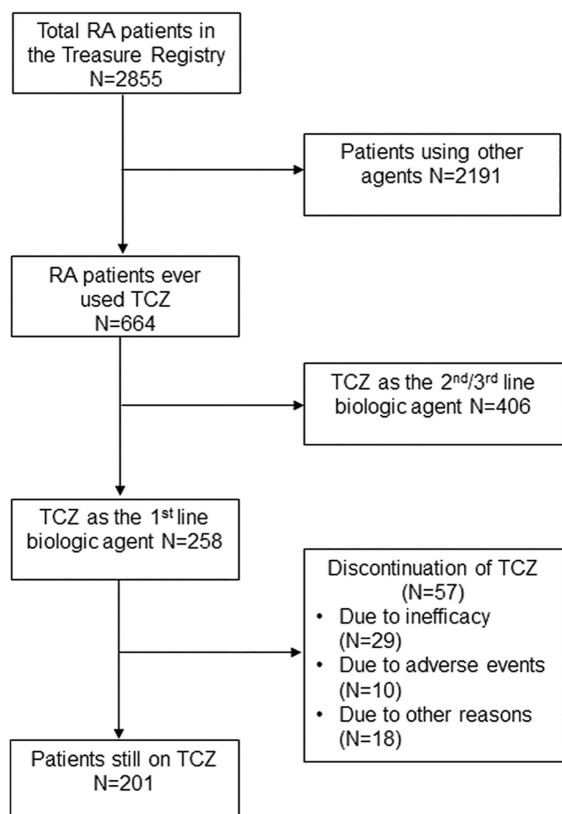
## Materials and methods

### Database and study population

The TReasure Registry, established in 2017, is a national, web-based, multi-centre, longitudinal, and observational database of RA and SpA patients on bDMARDs or tsDMARDs in Turkey. As of December 2020, there was a total of 8431 patients registered in the TReasure database. Of those, 2855 patients were diagnosed with RA by the treating physicians, and all RA patients fulfilled the 1987 American College of Rheumatology (ACR) and/or the 2010 European League against Rheumatism (EULAR)/ACR classification criteria. All patients using TCZ (ever) were screened in the database. Subsequently, those using TCZ as the first bDMARD were included in the analysis (Fig. 1).

### Data collection and outcome measures

The following data were collected: demographics, clinical, and laboratory features including age, sex, disease duration, TCZ treatment duration, use of csDMARDs and corticosteroids before and together with TCZ treatment, reasons for TCZ discontinuation (if discontinued), smoking status (if ever), rheumatoid factor (RF) and anti-CCP (anti-cyclic citrullinated peptide) positivity, erythrocyte sedimentation rate (ESR, mm/h), and C-reactive protein (CRP, mg/L). Outcome measures were disease activity score (DAS) 28, sim-



**Fig. 1.** Flow chart of rheumatoid arthritis (RA) patients using tocilizumab (TCZ) in the TReasure registry.

the Ethics Committee of Hacettepe University (KA17/058, May 2017) and Republic of Turkey, Ministry of Health (93189304-14.03.01, October 2017).

#### Statistical analysis

Data analyses were performed using the PASW Statistics for Windows, version 18.0. (SPSS Inc. Chicago, IL, USA). Categorical data including categories of continuous data are presented in frequency tables. Continuous data were described by number of non-missing values, number of missing values, median, mean, standard deviation, minimum, maximum, and 25<sup>th</sup> (Q1) and 75<sup>th</sup> (Q3) percent quartiles. Continuous variables were described by each visit and as change from baseline per time of analysis, if applicable. To evaluate the overall change in a continuous variable during visits (between baseline and 6<sup>th</sup> month and between baseline and 12<sup>th</sup> month), the Wilcoxon signed-rank test was performed. Comparisons of numerical parameters between independent prognostic groups were performed using the Mann-Whitney U-test and comparisons of categorical parameters were performed using the Chi-square test and in case Chi-square test assumptions were not met, Fisher's exact test was used. Time-to-event analyses for treatment retention were performed using the Kaplan-Meier method. Comparison of retention rates between the monotherapy and combined therapy groups was performed using the log rank test. A *p*-value of <0.05 was considered statistically significant.

## Results

### General characteristics of the patients

Of 2855 RA patients using bDMARDs or tsDMARDs recorded in the TReasure database, 642 patients have ever used TCZ. Of those, 258 used TCZ as their first bDMARD and were included in the analyses. The mean age of the patients was 54.4±13.1 years, median disease duration was 97 (60–179) months and majority of the patients were women (82%). The most commonly used csDMARDs before and in combination with TCZ were methotrexate (70% vs.

plified disease activity index (SDAI), clinical disease activity index (CDAI), visual analogue scale-patient global assessment (VAS-PGA; 0–100 mm) score, VAS-doctor global assessment (VAS-DGA; 0–100 mm) score, health assessment questionnaire-disability index (HAQ-DI) scores. Patients were categorised as remission, low disease activity (LDA), moderate disease activity (MDA) and high disease activity (HDA) according to the DAS28, CDAI, and SDAI scores (12). All parameters were evaluated at the time of initiation of TCZ treatment, at the 6<sup>th</sup> and 12<sup>th</sup> month visits.

### Response to tocilizumab treatment

Having DAS28 scores of 3.2 or less with reductions in DAS28 of more than 1.2 units as defined by European League Against Rheumatism was classified as good response to TCZ treatment (13). A CDAI score of 10 or less was defined as low disease activity and 2.8 or less as remission. A 50% improvement in the CDAI (CDAI50%) (14) was classified as minor response, and CDAI-major treatment response was defined as CDAI50% with a CDAI

of less than 10.1 (15). A SDAI score of 11 or less was defined as low disease activity and 3.3 or less as remission (14), and an improvement of 22 or more in SDAI was defined as major improvement (16). HAQ-DI scores between 0 and 0.5 were defined to represent mild physical function difficulty (17). An improvement of 0.22 units or more in the HAQ-DI score from baseline was considered a favourable response to TCZ treatment (18).

Comparison of the subgroups, TCZ monotherapy (TCZ mono) versus TCZ and csDMARD combination (TCZ combo) was performed in terms of baseline characteristics and outcome measures at the 6<sup>th</sup> and 12<sup>th</sup> months.

Drug retention was assessed as the time to definite treatment interruption. Reasons for TCZ discontinuation were analysed and classified into three major categories: 1. inefficacy (including primary and secondary); 2. adverse events (including infection, skin or systemic reactions, haematologic side effects etc.); and 3. other reasons (such as doctor or patient preference, inability to reach medicine or doctor, change in hospital). The study protocol was approved by

**Table I.** General characteristics and treatments of the patients (n=258) and general characteristics and treatments according to tocilizumab monotherapy (n=80) and combined therapy (n=178).

Features	Value	Features	TCZ-mono (n=80)	TCZ-combo (n=178)	p-value
Female/male, %	81.8/18.2	Female/Male, %	80/20	83/17	0.62
Mean age, years, mean±SD	54.41±13.09	Mean age, years, mean±SD	57.65 ± 11.6	52.96 ± 13.48	<b>0.008*</b>
RF and/or anti-CCP positivity, n (%)	201 (78.2)	RF and/or anti-CCP positivity, n (%)	60 (76)	141 (80)	0.56
Smoking (ever), n (%)	100/253 (39.5)	Smoking (ever), n (%)	26/76 (34.2)	74/177 (41.8)	0.26
Median disease duration, months (Q1-Q3)	97 (60-179)	Median disease duration, months, (Q1-Q3)	143 (72-214)	92 (55-158)	<b>0.001*</b>
csDMARD usage before TCZ, n (%)		csDMARD usage before TCZ, n (%)			
Hydroxychloroquine	163 (63.2)	Hydroxychloroquine	32 (40)	131 (73.6)	<b>&lt;0.001*</b>
Leflunomide	100 (38.8)	Leflunomide	23 (28.7)	77 (43.3)	<b>0.027*</b>
Methotrexate	181 (70.2)	Methotrexate	34 (42.5)	147 (82.6)	<b>&lt;0.001*</b>
Sulfasalazine	100 (38.8)	Sulfasalazine	21 (26.3)	79 (44.4)	<b>0.006*</b>
Median follow-up on TCZ, months (Q1-Q3)	15 (6-28)	Baseline DAS28-CRP, median (Q1-Q3)	4.85 (3.6-5.7)	5.01 (3.8-5.9)	0.4
Use of TCZ as monotherapy, n (%)	80 (31)	Baseline CDAI, median (Q1-Q3)	24.5 (19.2-31.2)	23 (16.5-32)	0.4
Use of TCZ in combination with csDMARDs, n (%)		Baseline SDAI, median (Q1-Q3)	37.5 (29-56.3)	50.4 (28.9-76.2)	<b>0.016*</b>
Hydroxychloroquine	110 (42.6)	Baseline HAQ-DI, median (Q1-Q3)	0.85 (0.62-1.2)	0.8 (0.6-1.2)	0.7
Leflunomide	73 (28.3)				
Methotrexate	94 (36.4)				
Sulfasalazine	27 (10.5)				
Use of TCZ in combination with steroids, n (%)	195 (75.6)				

TCZ: tocilizumab; SD: standard deviation; RF: rheumatoid factor; CCP: cyclic citrullinated peptide; csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs; DAS: Disease Activity Score; CRP: C-reactive protein; CDAI: Clinical Disease Activity Index; SDAI: Simplified Disease Activity Index; HAQ-DI: Health Assessment Questionnaire Disability Index.

**Table II.** The change in disease activity scores of the patients at the 6<sup>th</sup> and 12<sup>th</sup> months of tocilizumab treatment.

	Baseline		6 <sup>th</sup> Month	p-value	Baseline		12 <sup>th</sup> Month	p-value
	n	Median (Q1-Q3)	Median (Q1-Q3)		n	Median (Q1-Q3)	Median (Q1-Q3)	
DAS28-CRP	179	5.12 (3.85-5.88)	2.3 (1.74-3.47)	<0.001	149	5.21 (3.82-5.96)	2.09 (1.67-2.71)	<0.001
DAS28-ESR	177	5.37 (4.53-6.24)	2.33 (1.46-3.55)	<0.001	149	5.42 (4.6-6.29)	2.09 (1.4-2.95)	<0.001
VAS-patient	179	80 (70-85)	30 (20-46)	<0.001	149	80 (70-85)	20 (10-40)	<0.001
Number of swollen joints	179	4 (2-6)	0 (0-1)	<0.001	149	4 (2-6)	0 (0-0)	<0.001
Number of tender joints	179	6 (3-12)	0 (0-4)	<0.001	149	6 (3-10)	0 (0-2)	<0.001
CDAI	179	24 (18-32)	7 (4-12)	<0.001	149	24 (18-32)	5 (3-9)	<0.001
SDAI	179	46 (30-72.9)	11 (6.6-20.09)	<0.001	149	46 (29.2-72.6)	8 (5.3-12.35)	<0.001
HAQ-DI score	178	0.8 (0.65-1.2)	0.3875 (0-0.9)	<0.001	148	0.8 (0.7-1.175)	0.3 (0-0.7)	<0.001

DAS: Disease Activity Score; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; VAS: visual analogue scale; CDAI: Clinical Disease Activity Index; SDAI: Simple Disease Activity Index; HAQ-DI: Health Assessment Questionnaire Disability Index.

36%) and hydroxychloroquine (63 vs. 43%). Moreover, majority (75.6%) of the patients were using corticosteroids in combination with TCZ (Table I).

*Retention rates of TCZ and reasons for discontinuation*

The median TCZ treatment duration was 15 (range, 6–28) months. TCZ drug retention rates at the 12<sup>th</sup>, 24<sup>th</sup>, 36<sup>th</sup> and 60<sup>th</sup> months were 81.1%, 73.8%, 66.2%, and 63.6%, respectively. There was no significant difference in retention rates of the monotherapy and combined therapy groups (log rank test, p=0.62) (Fig. 2).

Of 258 patients, 57 (22%) were switched to other bDMARDs. Most of the reasons for switching were ineffi-

cacy in 26 (46%) (16 primary and 10 secondary) patients and side effects in 10 (17.5%).

*Response to tocilizumab treatment*

The DAS28, CDAI, SDAI, VAS, the number of swollen and tender joints, and HAQ scores of the patients were significantly lower at the 6<sup>th</sup> and 12<sup>th</sup> months of TCZ treatment compared with baseline (Table II).

At the 6<sup>th</sup> month of TCZ treatment, 70.4%, 67.6%, and 50.3% of the patients achieved remission and/or LDA according to DAS28, CDAI, and SDAI, respectively. More favourable results were observed at the 12<sup>th</sup> month evaluation with 85.5%, 84.9%, and 67.8% achieving remission and/or LDA ac-

cording to DAS28, CDAI, and SDAI, respectively (Fig. 3). Similarly, EULAR-good response was achieved in 59% and 73.7% of the patients at the 6<sup>th</sup> and 12<sup>th</sup> months of TCZ treatment.

While CDAI-major treatment response at 6 and 12 months was 60% and 79.6%, SDAI major improvement at 6 and 12 months was 68% and 69.8%, respectively. A favourable response in HAQ-DI score was also achieved at the 6<sup>th</sup> (68%) and 12<sup>th</sup> months (73%) of TCZ treatment.

*Comparison of subgroups (TCZ-mono vs. TCZ-combo)*

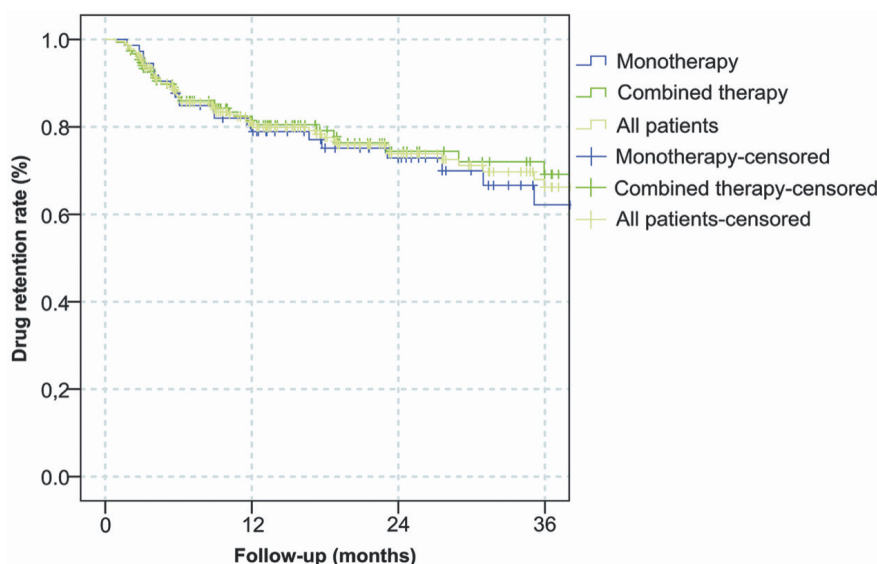
While 178 (69%) patients used TCZ in combination with csDMARDs, 80 (31%) of the patients used TCZ as



**Table III.** Favourable response of disease activity scores to tocilizumab treatment

	6 <sup>th</sup> Month			12 <sup>th</sup> Month			p1	p2
	All	TCZ-mono	TCZ-combo	All	TCZ-mono	TCZ-combo		
DAS28 ≤3.2 and ΔDAS28 >1.2, 105/179 (59) positive/total (%)		38/61 (62.3)	67/118 (56.8)	112/152 (73.7)	47/59 (79.7)	65/93 (70)	0.48	0.18
CDAI ≤10, positive/total (%)	121/179 (67.6)	40/61 (65.6)	81/118 (68.6)	129/152 (85)	53/59 (89.8)	76/93 (81.7)	0.67	0.17
CDAI 50% improvement, positive/total (%)	133/173 (77)	48/61 (78.7)	85/112 (76)	120/142 (84.5)	50/55 (91)	70/87 (80.5)	0.67	0.09
CDAI 50% improvement and CDAI ≤10.1, positive/total (%)	103/173 (60)	39/61 (64)	64/112 (57)	113/142 (79.6)	49/55 (89.1)	64/87 (73.6)	0.38	<b>0.02*</b>
SDAI ≤11, positive/total (%)	90/179 (50)	32/61 (52.5)	58/118 (49.2)	103/152 (67.8)	41/59 (69.5)	62/93 (66.7)	0.67	0.71
ΔSDAI ≥22, positive/total (%)	122/179 (68)	41/61 (67.2)	81/118 (68.6)	104/149 (69.8)	38/58 (65.5)	66/91 (72.5)	0.84	0.36
HAQ-DI score <0.5 units, positive/total (%)	107/179 (59.8)	40/61 (65.6)	67/118 (56.8)	100/152 (65.8)	40/59 (67.8)	60/93 (64.5)	0.25	0.68
ΔHAQ-DI ≥0.22, positive/total (%)	121/178 (68)	46/61 (75.4)	75/117 (64.1)	108/148 (73)	43/58 (74.1)	65/90 (72.2)	0.12	0.8

\**p*<0.05; *p*1: *p*-value between monotherapy and combined therapy at the 6<sup>th</sup> month; *p*2 value: *p*-value between monotherapy and combined therapy at the 12<sup>th</sup> month. TCZ: tocilizumab; DAS: Disease Activity Score; CDAI: Clinical Disease Activity Index; SDAI: Simple Disease Activity Index; HAQ-DI: Health Assessment Questionnaire Disability Index.



**Fig. 2.** Retention rate of tocilizumab (TCZ) treatment in rheumatoid arthritis patients (*p*=0.62; log rank test between monotherapy and combined therapy groups).

monotherapy. The TCZ-mono group was older, had a longer disease duration compared to the TCZ-combo group. csDMARD usage before TCZ was higher in the TCZ-combo group. At baseline, all disease activity parameters were comparable except median SDAI (higher in the TCZ-combo) (Table I).

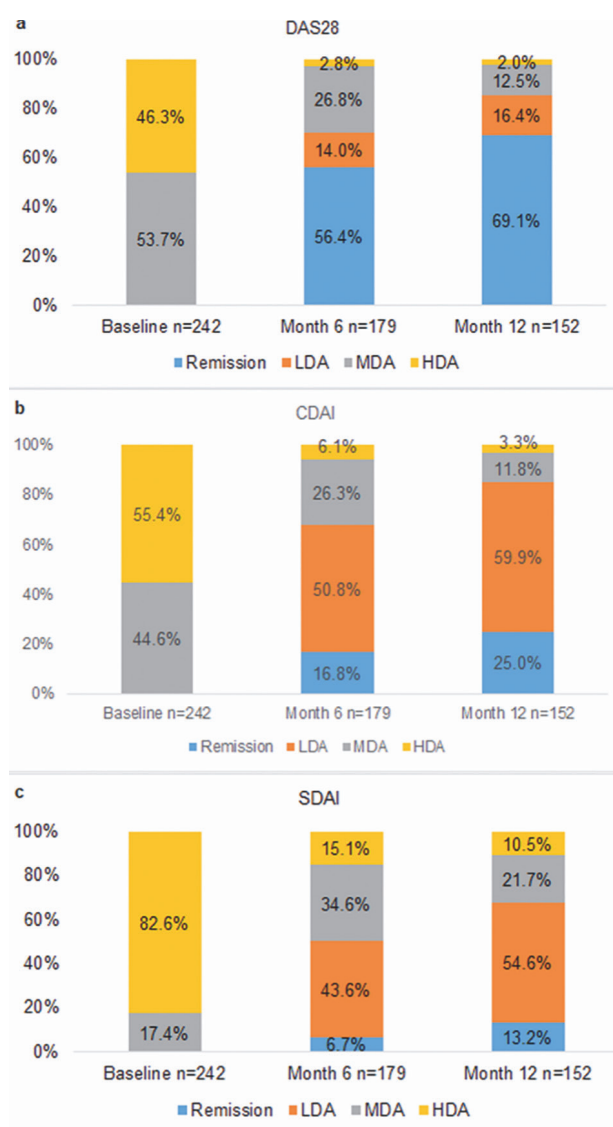
Similar efficacy was observed in both TCZ-mono and TCZ-combo subgroups according to all disease activity parameters at the 6<sup>th</sup> and 12<sup>th</sup> months of treatment (Table III). Furthermore, CDAI major response was significantly higher in the TCZ-mono group at the 12<sup>th</sup> month (89% and 73%, *p*=0.02).

**Discussion**

The current real-life TReasure study evaluated the long-term efficacy and drug retention rate of TCZ used as monotherapy or combined with csDMARDs in biologic-naive RA patients. At the 6<sup>th</sup> month evaluation, two thirds of the patients achieved remission or low disease activity in all disease activity parameters. These favourable results were observed in much more patients at 12<sup>th</sup> month. Baseline disease activity parameters were comparable between TCZ-mono and TCZ-combo groups, and similar favourable outcomes were achieved in both groups. Over 80% of the patients were still on TCZ treatment

at 12<sup>th</sup> month and no difference was found between TCZ-mono and combo groups.

The efficacy of TCZ in RA has been demonstrated in randomised controlled trials (RCTs) both in patients using TCZ in combination with csDMARDs / methotrexate or as monotherapy in patients who previously failed a csDMARD / methotrexate or TNFi (19-22). TCZ has also been shown to be effective and safe in real-life studies in patients with inadequate response to csDMARDs and/or TNFi (23-26). In the current study, of the 642 patients who had used TCZ as first or subsequent bDMARDs, 258 (39%) were initiated on TCZ as a first-line biologic. In similar multicentre retrospective studies, the percentage of patients who used TCZ as first line biologic treatment was found to be 22% in the British Society for Rheumatology Biologics Registry for RA (BSRBR-RA) (patients in 2010–2015) (25) and 36% in the Italian biologics’ registry Gruppo Italiano Studio Early Arthritis (GISEA) (patients in 1999–2014) (26). TCZ use as a first-line biologic was found to be slightly higher in the present study. TCZ, which was approved in 2009, was mostly used in TNFi inadequate responder patients in the first years and when TCZ had a place in the same step as other bDMARDs in the treatment guidelines; it was used more as the first treatment option in the following years. In the current study, TCZ was found to



**Fig. 3.** Categorisation of the patients according to disease activity scores DAS28 (a), CDAI (b), and c SDAI (c) at baseline, and at the 6<sup>th</sup> and 12<sup>th</sup> month.

DAS: Disease Activity Score; LDA: low disease activity; MDA: moderate disease activity; HDA: high disease activity; CDAI: Clinical Disease Activity Index; SDAI: Simple Disease Activity Index. DAS28: remission, <2.6; LDA, ≤3.2; MDA, ≤5.1; HDA, >5.1. SDAI: remission, ≤3.3; LDA, ≤11.0; MDA, ≤26.0; HDA, >26.0. CDAI: ≤2.8; LDA, ≤10.0; MDA, ≤22.0; HDA, >22.0

be quite effective in improving disease activity parameters at both 6<sup>th</sup> and 12<sup>th</sup> months compared to baseline, and high rates were observed in the categorical proportions of patients achieving remission and LDA according to DAS28, CDAI and SDAI at 6<sup>th</sup> and 12<sup>th</sup> months: proportions of patients achieving remission / LDA according to DAS28, CDAI and SDAI in patients using TCZ, were, 56/14%, 17/50%, 7/44% at month 6; and 69/16%, 25/60%, 13/54% at month 12, respectively.

In Phase III RCTs, the proportion of patients achieving DAS28 remission was 27% in the OPTION study (27) at

the 6<sup>th</sup> month, 47% in the LITHE study (28) at the 12<sup>th</sup> month, and 30% in the TOWARD study (29) at the 6<sup>th</sup> month. In real-life studies, the percentage of first-line TCZ users who achieved DAS28 remission was 42% in the BSRBR-RA study (25). In the German cohort (ROUTINE study) (23), the total percentage of first-line TCZ patients who achieved DAS28 remission and LDA was 71 and 52%, respectively, at 24 weeks and 66% at 52 weeks, and also CDAI LDA and CDAI remission were achieved by 57% and 18% of patients, respectively, at the 24<sup>th</sup> week. In a prospective study in Spain (24), 12% of the patients using

TCZ achieved DAS28 LDA and 46% achieved DAS28 remission at 6<sup>th</sup> month which was maintained for 52 weeks in 69% of the patients. In the Portugal national biologic registry (30), proportions of first-line TCZ patients achieving DAS28, CDAI, SDAI LDA were 77, 74 and 74%, respectively, at the 6<sup>th</sup> month. In the current study, the percentage of EULAR good responders was 59% and 74% at 6<sup>th</sup> and 12<sup>th</sup> months, respectively. In the RCTs, EULAR good or moderate responders was 82% in the TOWARD study (29), 68% in the RADIATE study (21) and 79% (38% good response) in the OPTION study (27). In the BSRBR-RA study (25), the percentage of EULAR good responders was 49% at the 6<sup>th</sup> month. In the German cohort (ROUTINE study) (23), 21% of the patients were using TCZ as first-line treatment, and the percentage of EULAR good responders was 55% at week 24, and 62% at week 52. In the Portugal national registry (30), the percentage of EULAR good responders was 64% at the 6<sup>th</sup> month. These results are similar/slightly higher to the Phase III RCTs and real-life studies. The differences and similarities of our study with RCTs and real-life studies may be due to study design, previous inadequate response to csDMARDs or TNFi, steroid use with TCZ, visual analogue scale score differences that may be affected by cultural factors, and percentage of patients using TCZ monotherapy and TCZ in combination with csDMARDs. TCZ as monotherapy may be a better treatment option when compared with other bDMARDs (31, 32). In our study, 31% of the patients used TCZ as monotherapy and it is compatible with other biological registers and studies of RA patients who receive bDMARDs as monotherapy (33, 34). While TCZ has demonstrated favourable efficacy in monotherapy in various studies especially compared to placebo, methotrexate monotherapy and other bDMARD monotherapy (35-39), there are few studies comparing TCZ monotherapy with TCZ and csDMARD combination therapy. In the current study, baseline disease activity parameters, except SDAI, and favourable response to TCZ treatment, except for CDAI

major response at the 12<sup>th</sup> month, were similar between the monotherapy and csDMARD combination groups. In an open-label, phase III study (40), the ROUTINE study (23), the ACT-LIFE (24) study, and the ICHIBAN study (41), similar efficacy with TCZ was demonstrated when used as monotherapy or in combination with csDMARDs, which is a similar finding observed in our study. Our study supports the high efficacy of TCZ as monotherapy.

In the current study, a high retention rate of TCZ was observed. The retention rates of TCZ at 12, 24, 36, and 60 months were 81%, 73%, 66%, and 59%, respectively. The percentage of switching to another bDMARD was 22%. The main reason for discontinuation was lack of efficacy (11%). There was no significant difference between the retention rates of monotherapy and combined treatment groups. The 1-year survival of TCZ users was 77% in the BSRBR-RA registry (25) and 82% in the ACT-LIFE study (24) at the 12<sup>th</sup> month and did not differ between patients treated as monotherapy or in combination in either study. In a prospective subcutaneous TCZ study (TANDEM study) (42), the rate of drug retention was estimated to be 64% at month 12, and no difference was observed between monotherapy and csDMARD combination treatment. In the prospective ACT-SOLO study (43), TCZ retention rate was 69% at the 12<sup>th</sup> month without difference between monotherapy and combination therapy. A global analysis published in 2019 (34) evaluated efficacy, safety and patterns of use of TCZ in real-world data from 16 countries, Kaplan-Meier estimates for the proportion of patients still receiving first-line TCZ was 81%. In an observational study using the FIRST registry (44), TCZ retention rate was 65% at month 36. In the Japan study by Nishimoto *et al.*, the retention rate of TCZ was 76% and 66% at months 36 and 60, respectively (45). As a measure of effectiveness, it is important to evaluate drug retention, as it reflects tolerability and patient satisfaction, especially in real-life. However, due to the fact that there are many factors affecting drug retention in real life (such as patient

compliance, national health system, economic reasons, cultural characteristics, comorbid diseases, monotherapy or combined treatment), proportion of retention rate in different registries may differ. Therefore, our results do not contradict the literature.

There are some limitations in the current study. Firstly, there are missing and incomplete data in several parameters due to retrospective nature of real-life studies. Secondly, data on TCZ dose and frequency were not evaluated. Thirdly, patients were not divided into subgroups in terms of subcutaneous and intravenous use, which may affect drug retention. On the other hand, our study also has important strengths. Firstly, the long-term effectiveness of TCZ in real-life was evaluated by comparing monotherapy and combined therapy. Secondly, all CDAI, SDAI, and DAS28 disease activity parameters were evaluated in terms of change from baseline and favourable treatment responses. Thirdly, drug retention was evaluated up to the fifth year.

In conclusion, in the TReasure Registry, 39% (258 patients) of patients used TCZ as first-line biologic treatment. Disease activity parameters showed a favourable response to TCZ treatment at 6 and 12 months compared to baseline. Of 258 first-line TCZ users, 80 (31%) used TCZ as monotherapy and 178 (69%) in combination with csDMARDs. Changes in DAS28, CDAI, SDAI and HAQ-DI scores from baseline to 6 and 12 months were significant and similar in both subgroups. The retention rate of TCZ at 12 and 60 months were quite high (81 vs. 59%) without difference between monotherapy and combination therapy subgroups.

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