Patterns of tocilizumab use, effectiveness and safety in patients with rheumatoid arthritis: core data results from a set of multinational observational studies

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Abstract

Objective

To observe patients with rheumatoid arthritis (RA) treated with the interleukin-6 receptor-alpha inhibitor tocilizumab (TCZ) in routine clinical practice.

Methods

Data on concomitant medications, effectiveness and safety were pooled from independent, multinational studies in patients with RA initiating intravenous TCZ according to local label recommendations observed in routine practice for 6 months. Patients were grouped by TCZ monotherapy or combination therapy with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs). The primary endpoint was the proportion of patients receiving TCZ after 6 months.

Results

Of 1336 patients enrolled, 506 (37.9%) received TCZ monotherapy and 830 (62.1%) received combination therapy. Kaplan-Meier analysis estimated that 80% (95% CI, 76%–83%) of monotherapy and 87% (95% CI, 84%–89%) of combination therapy patients continued to receive TCZ at 6 months (log-rank p<0.001). During the observation period, TCZ was discontinued by 113 (22.3%) monotherapy patients and 116 (14.0%) patients on combination therapy. The mean prednisone-equivalent oral corticosteroid dose was 8.4 mg/day for monotherapy and combination therapy patients at baseline and 7.7 and 7.6 mg/day, respectively, at month 6. Adverse events or laboratory abnormalities requiring TCZ dose modification were reported for 66 (13.0%) monotherapy and 130 (15.7%) combination therapy patients. Effectiveness at 6 months was similar between groups; mean (SD) change from baseline in Clinical Disease Activity Index (CDAI) was -20.3 (14.18) for monotherapy and -22.3 (16.09) for combination therapy (p=0.7347).

Conclusion

In routine clinical practice, 38% of patients received TCZ as monotherapy. Persistence on monotherapy or in combination therapy with csDMARDs was high, with a slight trend towards a higher rate with combination therapy, and effectiveness was similar between groups.

Key words

rheumatoid arthritis, biologic factors, humanised monoclonal antibodies, anti-rheumatic drugs

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Introduction

Current treatment recommendations for rheumatoid arthritis (RA) support the use of biologic disease-modifying anti-rheumatic drugs (bDMARDs) in combination with methotrexate or other conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) or as monotherapy to achieve low disease activity or remission (1, 2). Based on observational data from routine practice, it is estimated that 25% to 30% of patients take bDMARDs as monotherapy (3, 4), with patients previously exposed to a bDMARD significantly more likely to initiate bDMARD monotherapy than those who never received a bDMARD (4).

Tocilizumab (TCZ) is a humanised antihuman monoclonal antibody directed against the α subunit of the receptor for interleukin-6 (5), a pleiotropic cytokine that plays a central role in local and systemic inflammation in RA (6-8). TCZ is indicated for the treatment of patients with RA who have had an inadequate response to one or more csDMARDs either as monotherapy or in combination with csDMARDs (9, 10). In the European Union, TCZ is also approved for the treatment of patients who are methotrexate naive (10).

The phase 3 clinical trial programme for TCZ demonstrated that it was effective for the treatment of the signs and symptoms of RA in combination with csDMARDs for patients who have had an inadequate response to csDMARDs or tumour necrosis factor-α (TNF-α) inhibitors (11-14). In additional trials, TCZ monotherapy was effective for patients who were methotrexate naive or intolerant of methotrexate or who had an inadequate response to methotrexate (15-18). TCZ in combination therapy with csDMARDs and as monotherapy demonstrated similar effectiveness and comparable safety profiles in an open-label study close to clinical practice in patients who were csDMARD or TNF-α inhibitor inadequate responders (19).

To observe the routine practice patterns of TCZ use, adherence to label recommendations, persistence, safety and effectiveness in different countries, a multinational umbrella project (ACT-UP) was initiated to pool data from several independent, non-interventional, observational, multicentre studies capturing the same set of core data in patients started on TCZ.

Patients and methods

Patients

The studies contributing to the ACT-UP umbrella project shared a set of design elements, patient selection criteria and core data. All were non-interventional studies from 16 countries and enrolled adult patients who were 18 years of age or older and had moderate to severe RA based on the revised 1987 American College of Rheumatology criteria (20). Patients who had received TCZ at the decision of their treating physician and in accordance with local label recommendations within 8 weeks before the enrolment visit could be included. Patients who had previously received TCZ in a clinical trial, for compassionate use or more than 8 weeks before enrolment were ineligible. Patients had to give their informed consent to be enrolled in the study. Patients could not be enrolled in an ongoing clinical trial and could not have received treatment with any investigational agent within 4 weeks (or five half-lives of the investigational agent, whichever was longer) before starting TCZ. Patients with a history of autoimmune disease or inflammatory joint disease other than RA or secondary Sjögren's syndrome were also excluded. There were no restrictions on concomitant medications except that they be prescribed according to the investigator's judgement and the local label for TCZ.

Study design

There was no prespecified TCZ dosing regimen in the individual observational studies contributing to ACT-UP except for studies in Sweden (which included patients from Sweden, Denmark and Norway) and Belgium, which planned to enrol only patients on TCZ monotherapy according to their local protocols. The dose and duration of TCZ treatment were determined according to the investigator's judgement and in accordance with local label recommendations as part of routine clinical practice. No additional visits were scheduled for

the study, no study-specific medications were administered, and no interventional procedures were performed outside routine clinical practice. Patients were observed in routine local practice for 6 months after they initiated TCZ.

Assessments

During the 6-month observation period, data were collected on concomitant medications, effectiveness outcomes (Disease Activity Score using 28 joints [DAS28], Clinical Disease Activity Index [CDAI] and European League against Rheumatism [EULAR] good/moderate responses), adverse events (AEs) and serious AEs (SAEs). The primary endpoint was the proportion of patients continuing TCZ at 6 months after treatment initiation. To be considered in the study at 6 months, patients had to have received a TCZ infusion during the 6-month window of observation (from study day 155 onwards or from study day 134 onwards if the study was completed as planned after the fifth tocilizumab infusion, which was possible in some studies) or had to have an efficacy measurement during the 6-month window of observation (study days 155-197). To be considered on TCZ at 6 months, patients had to receive a TCZ infusion from study day 155 onwards or from study day 134 onwards if the study was completed as planned. Analysis was also performed for patients who had a TCZ dose after day 155 (original 6-month window). Secondary endpoints included treatment patterns over the 6 months from initiation of TCZ, effectiveness over time – including dosing schedule – combination csDMARD therapy, prednisone use and rates of AEs and SAEs. System organ class (SOC) and preferred terms for AEs and SAEs were assigned using the Medical Dictionary for Regulatory Activities, v. 18.1.

Statistical analysis

A preplanned pooled analysis was performed with patient-level data from all subjects in 14 studies conducted across 16 countries (Supplementary Table I). The ACT-UP analysis population included all patients from the studies who received at least one dose of TCZ. For the current analysis, patients were grouped as those who received TCZ in combination with a csDMARD (combination therapy) and those who received TCZ as monotherapy at baseline (defined as their first dose). Analyses primarily used descriptive statistical methods. In selected cases, statistical tests and modelling techniques such as analysis of covariance and Cox regression were used. Statistical tests were exploratory and were conducted at the 5% significance level without adjustment for multiplicity. Corresponding 95% confidence intervals (CIs) were presented for selected estimates. There was no imputation of missing data.

Results

Patient disposition and characteristics

As of 11 April 2015, 1336 patients were enrolled in 14 studies across 16 countries (Supplementary Table I) and received at least one dose of TCZ. Of these patients, 506 (37.9%) received TCZ as monotherapy and 830 (62.1%) received TCZ in combination with a csDMARD. If, however, the studies that planned to enrol only patients receiving TCZ monotherapy according to their local protocols (Sweden and Belgium) were excluded, a total of 1161 patients were enrolled, 333 (28.7%) of

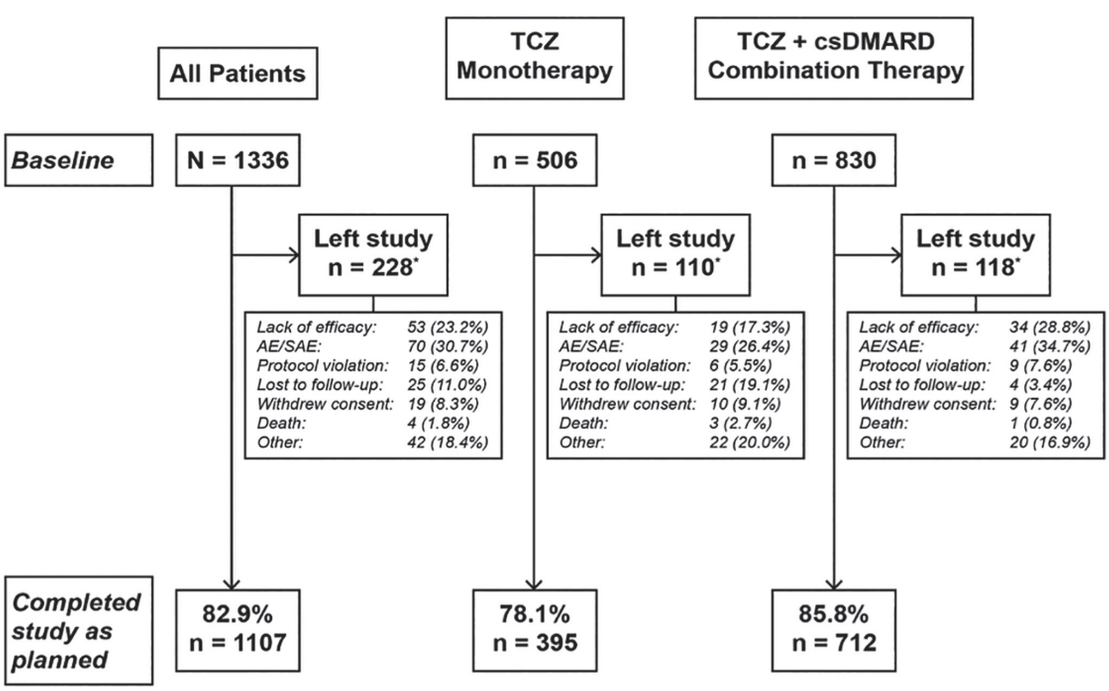

Fig. 1. Patient disposition.
AE: adverse event; csDMARD: conventional synthetic disease-modifying anti-rheumatic drug; SAE: serious adverse event; TCZ: tocilizumab.
*n=number of patients who prematurely terminated the study (for one monotherapy patient, reason was unknown).
Reasons reported for one patient are included as 'other'.

whom received monotherapy. A protocol violation in the Swedish study led to the enrolment of two patients receiving combination therapy. The proportion of patients who completed the study as planned was 82.9% (1107/1336) overall: 78.1% (395/506) in the monotherapy group and 85.8% (712/830) in the combination therapy group (Fig. 1). The proportion of patients remaining in the study in the 6-month window from day 134 was 85.0% (1135/1336) overall: 79.8% (404/506) in the monotherapy group and 88.1% (731/830) in the combination therapy group. Baseline demographics and disease characteristics were similar between the monotherapy group and the combination therapy group (Table I).

Table I. Baseline demographics and disease characteristics.

Parameter	TCZ monotherapy n=506	TCZ + csDMARD combination therapy n=830	All patients N=1336
Age, years	55.2 (13.2) n=504	54.9 (12.7) n=830	55.0 (12.9) n=1334
Female, n (%)	398 (78.8) n=505	685 (82.5) n=830	1083 (81.1) n=1335
Disease duration, years	10.7 (10.4) n=501	9.7 (8.9) n=821	10.1 (9.5) n=1322
RF positive, n (%)	302 (59.8) n=505	506 (61.0) n=829	808 (60.6) n=1334
Structural joint damage, n (%)	287 (56.8) n=505	444 (53.6) n=829	731 (54.8) n=1334
Patient Pain VAS, mm	63.6 (22.5) n=434	63.6 (23.1) n=725	63.6 (22.9) n=1159
Patient Assessment of Disease Activity VAS, mm	65.6 (20.9) n=448	65.7 (23.0) n=733	65.7 (22.2) n=1181
Physician Assessment of Disease Activity VAS, mm	57.4 (22.9) n=377	61.3 (21.1) n=702	59.9 (21.8) n=1079
Fatigue VAS, mm	61.6 (23.8) n=302	63.6 (24.4) n=641	62.9 (24.2) n=943
CRP, mg/L	21.1 (30.9) n=437	22.0 (31.4) n=708	21.7 (31.2) n=1145
ESR, mm/h	36.2 (27.3) n=407	36.2 (25.3) n=718	36.2 (26.0) n=1125
TJC28	11.0 (7.3) n=469	12.8 (7.6) n=763	12.1 (7.5) n=1232
SJC28	7.3 (5.8) n=467	8.1 (6.1) n=763	7.8 (6.0) n=1230
HAQ-DI*	1.6 (0.7) n=355	1.6 (0.7) n=678	1.6 (0.7) n=1033
DAS28†	5.6 (1.2) n=419	5.9 (1.2) n=691	5.7 (1.2) n=1110
CDAI	31.5 (13.2) n=358	34.1 (14.0) n=674	33.2 (13.8) n=1032
SDAI	33.6 (14.3) n=317	36.5 (14.6) n=603	35.5 (14.5) n=920
Baseline corticosteroid use, n (%)	226 (44.7) n=506	483 (58.2) n=830	709 (53.1) n=1336
Previous biologic exposure, n (%)	308 (60.9) n=506	484 (58.3) n=830	792 (59.3) n=1336

CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; DAS28: Disease Activity Score using 28 joints; ESR: erythrocyte sedimentation rate; HAQ-DI: Health Assessment Questionnaire-Disability Index; SDAI: Simplified Disease Activity Index; SJC28: swollen joint count at 28 joints; TJC28: tender joint count at 28 joints; TCZ: tocilizumab; VAS: visual analogue scale.
Data are mean (SD) unless otherwise noted. Not all patients had complete sets of data because of the observational nature of the study; therefore, the numbers of patients with data available for each characteristic differ.
*HAQ-DI data from Belgian patients were excluded because of use of an alternative scoring system.
†DAS28-ESR or, if missing, DAS28-CRP.

Tocilizumab treatment

Most patients in both the monotherapy (478/506 [94.5%]) and the combination therapy (791/830 [95.3%]) groups started TCZ at a dose of 8 mg/kg. TCZ was started at a dose of 4 to 7 mg/kg in 4.7% (24/506) of monotherapy patients and 4.3% (36/830) of combination therapy patients. Only four patients in the monotherapy group and three patients in the combination therapy group (0.8% and 0.4%, respectively) started TCZ at a dose greater than 8 mg/kg.

Kaplan-Meier estimates for analysis of the proportion of patients still receiving TCZ at 6 months (24 weeks), in which patients who completed the study as planned were censored, were 80% (95% CI, 76%–83%) for monotherapy and 87% (95% CI, 84%–89%) for combination therapy ($p<0.001$, log-rank test). Kaplan-Meier curves for persistence on TCZ are shown in Figure 2. In Cox regression analyses when additional factors (sex, country, disease duration, age, baseline DAS28, previous biologic exposure, corticosteroid use at baseline and seropositivity at baseline) were included in the model, the hazard ratio for continuing TCZ monotherapy versus combination therapy was 0.64 ($p=0.0118$; Supplementary Table II).

In the 6-month window from day 134, 393/506 (77.7%) monotherapy patients and 714/830 (86.0%) combination therapy patients received at least one dose of TCZ. Of these, 92.4% (363/393) of monotherapy patients and 93.3% (666/714) of combination therapy patients were receiving TCZ at 8 mg/kg; 7.1% (28/393) and 6.2% (44/714), respectively, were receiving TCZ at 4-7 mg/kg; and two monotherapy patients (0.5%) and four combination therapy patients (0.5%) were receiving TCZ at >8 mg/kg.

During the 6-month observation period, 49 (9.7%) patients in the monotherapy group and 85 (10.2%) patients in the combination therapy group changed their TCZ dose. In the monotherapy group, 10 patients (2.0%) increased their dose, 21 patients (4.2%) decreased their dose and 18 patients (3.6%) both increased and decreased their dose. In

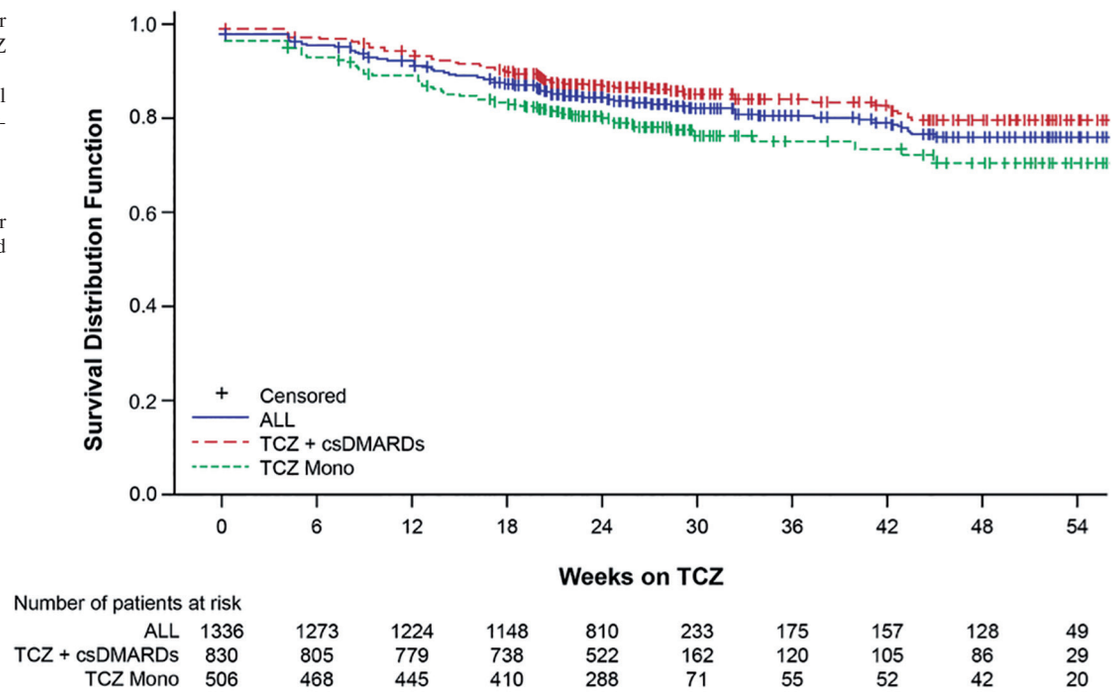

Fig. 2. Kaplan-Meier curve of duration on TCZ (first to last dose). csDMARD: conventional synthetic disease-modifying anti-rheumatic drug; Mono: monotherapy; TCZ: tocilizumab. Data were censored for patients who completed the study as planned.

the combination therapy group, 11 patients (1.3%) increased their dose, 27 patients (3.3%) decreased their dose and 47 patients (5.7%) both increased and decreased their dose. Reasons for TCZ dose changes were AEs (including clinically significant laboratory abnormalities) in 46.9% (23/49) of patients in the monotherapy group and 44.7% (38/85) of patients in the combination therapy group and lack of efficacy in 14.3% (7/49) of patients in the monotherapy group and 3.5% (3/85) of patients in the combination therapy group.

TCZ was discontinued by 229/1336 (17.1%) of patients overall: 113/506 (22.3%) in the monotherapy group and 116/830 (14.0%) in the combination therapy group over the 6-month observation period. Reasons for TCZ discontinuation were lack of efficacy for 19.5% (22/113) of patients in the monotherapy group and 28.4% (33/116) of patients in the combination therapy group. TCZ discontinuations because of AEs (including clinically significant laboratory abnormalities) were similar between the groups: 34.5% (39/113) of patients in the monotherapy group and 35.3% (41/116) of patients in the combination therapy group. Additional reasons for discontinuation included unknown (monotherapy, 15.0% [17/113]; combination therapy, 17.2% [20/116]) and other (monotherapy, 31.0% [35/113]; combination therapy, 19.0% [22/116]). Other reasons were withdrawal of consent, non-compliance, patient decision, lost to follow-up, pregnancy, lack of funding and surgery.

Table II. Concomitant methotrexate use and dose all patients* and concomitant corticosteroid use and dose by treatment group.

	Patients on drug at baseline, n (%)	Mean dose at baseline (median [range])†‡§	Mean dose at 6 months (median [range])†‡§
Methotrexate			
All patients n = 1336	576 (43.1)	15.7 (15.0 [2.5-25.0])	15.2 (15.0 [2.5-25.0])
Corticosteroids (prednisone-equivalent dose)			
TCZ monotherapy n = 506	204 (40.3)	8.4 (7.5 [1.0-30.0])	7.7 (5.5 [1.0-30.0])
TCZ + csDMARD combination therapy n=830	427 (51.4)	8.4 (5.0 [1.5-50.0])	7.6 (5.0 [1.3-50.0])

TCZ: tocilizumab.
*All patients regardless of treatment subgroup.
†mg/week for methotrexate and mg/day (prednisone-equivalent dose) for corticosteroids.
‡For corticosteroids, data are from the subset of patients for whom corticosteroid dose, unit, frequency and route (oral or missing) data were available.
§For methotrexate, data are median (range) dose in patients for whom methotrexate, unit and frequency data were available.

Concomitant treatments

Methotrexate was the most common concomitant csDMARD. It was used by 78.9% (655/830) of patients in the combination therapy group at a mean dose of 15.7 mg/week. Other csDMARDs used by this group included hydroxychloroquine (27.6% [229/830]), leflunomide (23.5% [195/830]), sulphasalazine (20.2% [168/830]), gold (1.8% [15/830]) and cyclosporine (1.6% [13/830]). Of note, 26 (5.1%) patients in the monotherapy group added a csDMARD after they initiated TCZ, and 60 (7.2%) patients in the combination therapy group stopped all csDMARDs during the study. The dose of methotrexate was changed in 11.9% (80/674) of patients during the 6-month observation period (Table II).

Corticosteroids (oral or parenteral) were used by 44.7% (226/506) of patients in the monotherapy group and 58.2% (483/830) of patients in the combination therapy group at baseline. The mean prednisone-equivalent dose of oral corticosteroids at baseline was 8.4 mg/day in both groups (Table II). Corticosteroid dose was decreased in 28.8% (65/226) of patients in the monotherapy group and in 22.4% (108/483) of patients in the combination therapy group, whereas the proportions of patients who increased their corticosteroid dose were similar in both groups (12.4% [28/226] of monotherapy patients and 10.4% [50/483] of combination therapy patients) (Fig. 3). At 6 months, the mean prednisone-equivalent dose was 7.7 mg/day and 7.6 mg/day in the monotherapy and combination therapy groups, respectively (Table II).

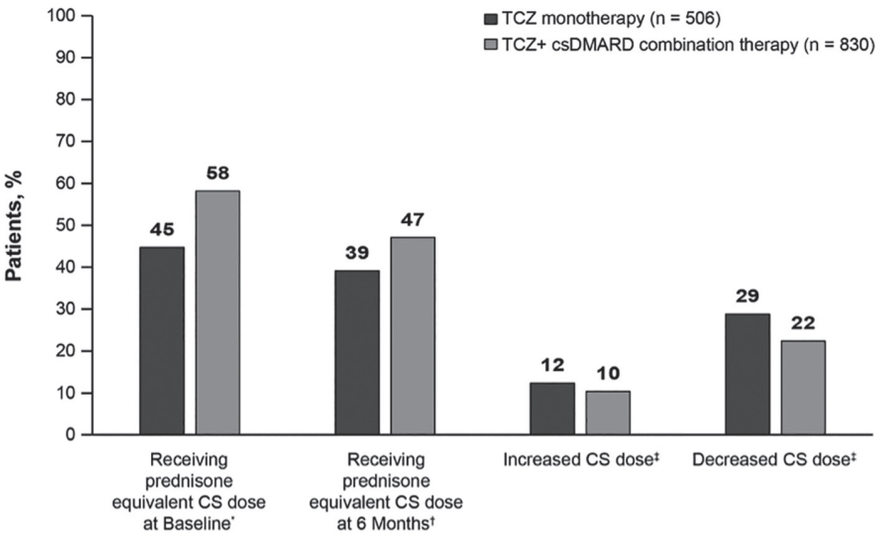

Fig. 3. Concomitant corticosteroid use by treatment group. CS: corticosteroid; TCZ: tocilizumab. *Percentage of total subgroup population. †Percentage of patients in the study at month 6. ‡Percentage of patients receiving CS at baseline.

Safety

Overall rates of AEs and SAEs were comparable between patients who received TCZ as monotherapy and those who received TCZ in combination with a csDMARD (Table III). In the monotherapy group, AEs and SAEs were reported at rates of 214/100 patient-years (PY) (95% CI, 197–232) and 23/100 PY (95% CI, 18–29), respectively. In the combination therapy group, AEs and SAEs were reported at rates of 207/100 PY (95% CI, 194-219) and 19/100 PY (95% CI, 15-23), respectively. Infections were the most common AEs and SAEs, and they occurred more frequently in the combination therapy group (19.9% [165/830] and 2.7% [22/830], respectively) than in the monotherapy group (17.6% [89/506] and 2.0% [10/506], respectively). AEs that led to withdrawal from study treatment were reported in 41 (8.1%) patients in the monotherapy group and 55 (6.6%) patients in the combination therapy group. No gastrointestinal perforations were reported in either group. Overall, five patients died during the study, three in the monotherapy group and two in the combination therapy group. Reasons for death were shock, arrhythmia and pneumonia in the monotherapy group and sepsis and cerebrovascular accident in the combination therapy group. None of the deaths were deemed by the investigator to be related to TCZ treatment.

AEs that necessitated dose modification or abnormal laboratory test results that required follow-up were reported in 66 (13.0%) patients in the monotherapy group and 130 (15.7%) patients in the combination therapy group. In these instances, investigators followed local label or protocol recommendations in 92.4% (61/65) of monotherapy and 96.2% (125/130) of combination therapy patient cases.

Effectiveness

The mean (SD) change from baseline to month 6 in DAS28 was -2.9 (1.47) in the monotherapy group (n=178) and -3.2 (1.65) in the combination therapy group (n=365) (p=0.9403 based on analysis of covariance [ANCOVA] that included baseline DAS28 in the model). The mean (SD) change from baseline in CDAI was -20.3 (14.18) in the monotherapy group (n=186) and -22.3 (16.09) in the combination therapy group (n=416) (p=0.7347 based on ANCOVA that included baseline CDAI in the model). Proportions of patients with a EULAR good or moderate response at 6 months was 94.4% (168/178) in the monotherapy group and 92.1% (336/365) in the combination therapy group (p=0.3242 based on chi-square test).

Discussion

In this multinational, observational study, 38% of patients (29% if monotherapy-only protocols are excluded) started TCZ as monotherapy in clinical practice, which is consistent with estimates of biologic monotherapy use reported from registry data (3). Previously, an open-label study resembling clinical practice (19), initiated before the efficacy of TCZ monotherapy in clinical trials was published (16, 17), reported that 14% of patients started TCZ monotherapy. In a recent observational clinical practice study of patients with inadequate response to csDMARDs (21), 28% of patients prescribed TCZ as their first biologic therapy received it as monotherapy, which is in line with the current study.

Persistence on TCZ was high in the current study; most patients who initiated TCZ (Kaplan-Meier estimate, 84%) continued to receive it after 6 months regardless of whether they started it as monotherapy or in combination with csDMARDs. However, persistence was slightly better for patients receiving combination treatment (absolute difference between groups at 6 months, 7%). This is in contrast to previous studies of TCZ, in which similar proportions of patients completed 6 months of TCZ monotherapy and combination therapy in a randomised controlled trial (22) and in an open-label uncontrolled trial (19).

Table III. Adverse events, serious adverse events and adverse events that led to withdrawal, by treatment group.

	TCZ monotherapy n=506	TCZ + csDMARD combination therapy n=830	All patients N=1336
AEs, n (%)	269 (53.2)	418 (50.4)	687 (51.4)
(no. events/100 PY [95% CI])	(214 [197-232])	(207 [194-219])	(209 [199-220])
AEs reported in ≥10% of patients, by SOC			
Infections and infestations	89 (17.6)	165 (19.9)	254 (19.0)
Musculoskeletal and connective tissue disorders	55 (10.9)	64 (7.7)	119 (8.9)
Investigations*	52 (10.3)	105 (12.7)	157 (11.8)
SAEs, n (%)	43 (8.5)	62 (7.5)	105 (7.9)
(no. events/100 PY [95% CI])	(23 [18-29])	(19 [15-23])	(20 [17-24])
SAEs of interest, by SOC, n (%)			
Infections and infestations†	10 (2.0)	22 (2.7)	32 (2.4)
(no. events/100 PY [95% CI])	(4 [1-6])	(5 [3-7])	(5 [3-6])
Cardiac disorders‡	6 (1.2)	4 (0.5)	10 (0.7)
Total AEs leading to withdrawal from study treatment, n (%) (no. events/100 PY [95% CI])	41 (8.1) (20 [15-26])	55 (6.6) (13 [10-17])	96 (7.2) (16 [13-19])
AEs leading to withdrawal from study treatment reported in ≥1% of patients, by SOC			
Skin and subcutaneous tissue disorders	6 (1.2)	9 (1.1)	15 (1.1)
Infections and infestations	7 (1.4)	10 (1.2)	17 (1.3)
Gastrointestinal disorders	6 (1.2)	2 (0.2)	8 (0.6)
General disorders and administration site conditions	6 (1.2)	6 (0.7)	12 (0.9)
Cardiac disorders	4 (0.8)	0	4 (0.3)
Blood and lymphatic system disorders	4 (0.8)	7 (0.8)	11 (0.8)
Neutropenia	1 (0.2)	3 (0.4)	4 (0.3)
Pancytopenia	1 (0.2)	2 (0.2)	3 (0.2)
Thrombocytopenia	2 (0.4)	0	2 (0.1)

n refers to number of patients with event. Rate per 100 PY is based on total number of events (multiple occurrences of the same event in a single patient were counted multiple times) during TCZ exposure, determined for each patient as (date of last TCZ dose + 28 days) minus date of first TCZ dose.
*Includes laboratory tests such as liver function tests, complete blood counts and lipid panels and includes assessments such as weight and blood pressure.
†Infection and infestation SAEs occurring in >1 patient by preferred term: pneumonia (monotherapy, 2 [0.4%]; combination therapy 3 [0.4%]), postprocedural infection (monotherapy, 0; combination therapy 2 [0.2%]), upper respiratory infection (monotherapy, 2 [0.4%]; combination therapy 2 [0.2%]), erysipelas (monotherapy, 0; combination therapy 2 [0.2%]).
‡Cardiac disorder SAEs occurring in >1 patient by preferred term: acute myocardial infarction (monotherapy, 1 [0.2%]; combination therapy 2 [0.2%]), myocardial infarction (monotherapy, 1 [0.2%]; combination therapy 1 [0.1%]).

Supplementary Table I.
Number of patients enrolled by country.

Country	All patients, n (%)*
Argentina	50 (3.7)
Australia	37 (2.8)
Belgium	68 (5.1)
Canada	198 (14.8)
Estonia	23 (1.7)
Finland	29 (2.2)
Greece	60 (4.5)
Hungary	290 (21.7)
Indonesia	43 (3.2)
Israel	184 (13.8)
Italy	151 (11.3)
Peru	16 (1.2)
Serbia	80 (6.0)
Sweden†	107 (8.0)
Total, n	1336

*Percentage of total across all regions.
†Sweden, Denmark, Norway.

Supplementary Table II.
Cox regression analysis of TCZ persistence.

Effect	Hazard ratio	*p*-value
Female	0.754	0.1168
Country (comparison *vs*. Sweden)		
Argentina	0.255	0.1906
Australia	0.661	0.4748
Belgium	0.384	0.0554
Canada	0.544	0.0519
Estonia	1.457	0.4096
Finland	0.644	0.4823
Greece	0.934	0.8617
Hungary	0.726	0.2916
Indonesia	1.351	0.4277
Israel	0.884	0.6951
Italy	0.455	0.0444
Peru	0.000	0.9770
Serbia	0.179	0.0066
Disease duration, years	1.002	0.7568
Age, years	0.993	0.2342
DAS28 at baseline	1.146	0.0371
Previous biologic exposure	0.963	0.8280
No corticosteroid use at baseline	1.036	0.8195
Not seropositive at baseline	1.250	0.1655
Combination therapy	**0.642**	**0.0118**

Patients with RA treated with TNF-α inhibitors have also been shown to have higher rates of persistence with combination therapy than with monotherapy, possibly because of the increased effectiveness of TNF-α inhibitors in combination with csDMARDs (23). However, the effectiveness of TCZ is similar for combination therapy and monotherapy, as demonstrated in this study and previous studies (19, 22). In patients who did discontinue TCZ treatment, the most common reason was AEs, with 35% of patients withdrawing in both the monotherapy and the combination therapy groups. Fewer patients discontinued TCZ because of lack of efficacy in the monotherapy group than the combination therapy group (19% *vs*. 28%), whereas more patients discontinued for "other" reasons in the monotherapy group (31%) than the combination therapy group (19%). Physicians reported high adherence to local label recommendations for dosing TCZ following laboratory abnormalities in clinical practice.

TCZ was well tolerated both as monotherapy and as combination therapy with csDMARDs. The safety profile in this observational study was similar to that reported previously in the clinical trial programme; no new safety signals were identified. Infections were the most frequently reported AEs and SAEs in both groups, which is consistent with reports from placebo-controlled periods and long-term extensions of the clinical trial programme (24) and in the previous study of TCZ use in a setting close to clinical practice (19).

Patients responded well to treatment with TCZ monotherapy and combination therapy with csDMARDs over the 6 months of the study. Effectiveness measures, including change in DAS-28_{ESR}, CDAI and EULAR good/moderate response rates, were similar between both groups. As in previous studies, comparable response rates were ob-

served between TCZ monotherapy and combination therapy with csDMARDs (19, 22, 25).

Overall, the results of this observational, multicentre study of TCZ in routine clinical practice in different countries show that results obtained in the clinical trial programme for TCZ are reproduced in a real-world setting.

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