Sustained effectiveness and safety of subcutaneous tocilizumab over two years in the ARATA observational study

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Abstract

Objective

To investigate long-term effectiveness and safety of subcutaneous tocilizumab (TCZ-SC) in the routine clinical care of patients with rheumatoid arthritis (RA).

Methods

ARATA (ML29087) was a prospective, multicentre, observational study of adult patients with active RA initiating therapy with TCZ-SC. The primary effectiveness outcome was the proportion of patients achieving DAS28-ESR <2.6 at week 104. Additional efficacy outcomes included individual DAS28-d_{crit} responses (improvement of ≥1.8 from baseline), CDAI remission (≤2.8), and patient-reported outcomes (PROs), including Work Productivity and Activity Impairment scores. Adverse event rates were used to evaluate safety and tolerability.

Results

Between May 2014 and July 2018, 114 study centres in Germany enrolled 1,300 patients with RA who received at least one dose of TCZ-SC (mean age 57.3 [SD 12.5] years, mean DAS28-ESR of 4.9 [SD 1.3]). At week 104, 58.7% (365/622) patients achieved DAS28-ESR <2.6, 64.0% had an individual DAS28-d_{crit} response, and 31.4% (241/767) achieved CDAI remission. PROs, including patient global assessment, pain, and fatigue, showed marked improvements from baseline. Work outcomes, including absenteeism (missed work) and presenteeism (productivity while at work), also improved. Injection reactions were rare and no new safety signals occurred. Patients expressed a high level of satisfaction with treatment. Baseline patient characteristics and outcomes were similar for ARATA and ICHIBAN (an observational study of TCZ-IV in Germany), despite different formulations and time periods.

Conclusion

The safety and effectiveness of TCZ-SC is maintained over 2 years during routine clinical care. TCZ-SC represents a convenient and effective option for RA patients who prefer SC administration.

Key words

rheumatoid arthritis, tocilizumab, biologic therapy, outcomes, safety

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Competing interests: see page 1471.

Introduction

Tocilizumab (TCZ) blocks interleukin (IL)-6 activity by binding to membrane-bound and soluble IL-6 receptors (1), thereby modulating multiple biologic pathways associated with inflammatory disorders (2, 3). TCZ is approved for rheumatoid arthritis (RA) treatment in both intravenous (IV) and subcutaneous (SC) formulations, either as monotherapy or in combination with methotrexate (MTX) (4). Dosing flexibility and schedules differ between the IV and SC formulations: TCZ-IV has flexible dosing based on weight (8 mg/kg up to 800 mg per infusion once every 4 weeks for adult RA patients) while TCZ-SC is administered at a set dose of 162 mg once per week (4). The SUMMACTA phase III trial demonstrated that TCZ-IV and TCZ-SC had comparable efficacy and safety in patients with RA and an inadequate response to disease-modifying anti-rheumatic drugs (DMARDs) (5, 6).

Observational studies add important information to data from randomised clinical trials on the use of agents in diverse clinical populations and on their long-term effectiveness and safety in routine care (7). In particular, observational studies are able to evaluate effectiveness in patients who may not be eligible for clinical trials – an estimated 56% to 96% of RA patients (8, 9). Because RA patients in everyday practice differ in clinical and demographic characteristics from those in randomised clinical trials (10), observational data are essential to understanding drug effectiveness and safety and tolerability during routine clinical care. Observational studies also provide a means of evaluating the impact of therapeutic strategies on "real world" outcomes such as work productivity.

The ARATA study was a prospective, multicentre, 2-year, non-interventional study of adult German patients with RA who initiated TCZ-SC during routine clinical care. Here we report on the safety and effectiveness of TCZ-SC over 2 years, including changes in disease activity, remission and response rates, patient-reported outcomes (PROs) including work productivity, adverse event (AE) rates, and patient satisfaction. These findings are placed into the context of data from a previously published German observational study on TCZ -IV, the ICHIBAN study (11, 12).

Methods

Study design

The ARATA study (ML29087) was a prospective, multicentre, single-arm, non-interventional study of German patients with RA (NCT02251860). The main objective of the ARATA study was to evaluate the effectiveness and safety of TCZ-SC up to week 104 in routine clinical care. TCZ-naive patients ≥18 years of age who had active RA based on clinician assessment and who initiated TCZ-SC in routine clinical care were eligible for study enrolment. The TCZ treatment decision was independent of and occurred prior to study inclusion. Enrolment was allowed for up to 1 month after the first TCZ administration as long as baseline parameters and disease characteristics were available. Treatment-naive patients and those who received TCZ-SC in combination with a conventional synthetic DMARD (csDMARD) other than MTX at baseline were excluded due to off-label use of TCZ-SC. Patients currently enrolled in interventional RA clinical trials were also excluded. All patients gave informed consent. Ethics approval was granted by the Ethics Commission of the Medical Department of Goethe University, Frankfurt am Main, Germany and the Medical Association of Rheinland-Pfalz, Mainz, Germany.

The TCZ-SC dose recommended in the Summary of Product Characteristics at that time was 162 mg once weekly and has not changed since then (4). In this observational study, the treating physician could, however, modify the TCZ doses. Information on concomitant therapies were collected at each visit.

An electronic Case Report Form (eCRF) was used to collect patient data. Demographic data were collected at baseline (before TCZ-SC initiation) and disease and treatment data were collected at baseline and during regular office visits, typically at weeks 4, 12, 24, 36, 52, 64, 76, 88, and 104. Patients were allowed to discontinue TCZ without discontinuing the study.

Outcomes

The primary effectiveness outcome was the proportion of patients achieving remission, defined by Disease Activity Score based on 28 joints (DAS28) and erythrocyte sedimentation rate (ESR) <2.6, at week 104 (13). Low disease activity (LDA) was defined as DAS28-ESR ≤3.2 (14). Analyses of disease activity based on the Clinical Disease Activity Index (CDAI) were also conducted, with remission defined as CDAI ≤2.8 (13) and LDA as ≤10 (15). A DAS28-ESR decrease ≥1.8 from baseline was defined as an individual therapeutic response based on the critical difference for improvement (DAS28-d_{crit}) (16).

PROs included two functional assessments, the Health Assessment Questionnaire Disability Index (HAQ-DI) on a scale of 0 (best) to 3 (worst) (17) and the validated Funktionsfragebogen Hanover (FFbH) functional ability questionnaire on a scale of 0 (total loss of functional capacity) to 100 (maximal functional capacity) (18). Pain, fatigue, sleep disturbance, and patient global assessment (PtGA) were measured on 100-mm visual analogue scales (VAS) ranging from 0 (best) to 100 (worst).

The validated Work Productivity and Activity Impairment (WPAI) questionnaire (19, 20) was used to measure four aspects of work productivity in the past 7 days: (1) absenteeism (% of missed work hours due to health problems); (2) presenteeism (impairment at work as assessed on a VAS ranging from 0 [no impairment] to 10 [complete impairment] converted to percent); (3) total work productivity impairment, an aggregate measure of absenteeism and presenteeism (calculated as absenteeism rate + [(1-absenteeism rate x presenteeism rate]); and (4) activity impairment due to health (assessed on a VAS ranging from 0 [no impairment] to 10 [complete impairment] converted to percent) (19, 20).

Safety evaluations were based on AE reports as coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 16.1 or higher. We assessed overall AE rates, AEs by system organ class (SOC), and AEs of special interest (infections including opportunistic infections, medically significant hepatic events, anaphylaxis, malignancies, bleeding events, myocardial infarction/acute coronary syndrome, gastrointestinal perforation and related events, demyelination events, and strokes).

At each visit, patients were asked to complete questions on whether they were satisfied with TCZ-SC, felt restricted by TCZ-SC, and would recommend TCZ-SC to other patients. They were also asked about their pain level during administration of TCZ-SC.

Comparisons between the ARATA and ICHIBAN (TCZ-IV) studies utilised data contained in the ICHIBAN publication (11) supplemented by data on file for variables that had not been reported.

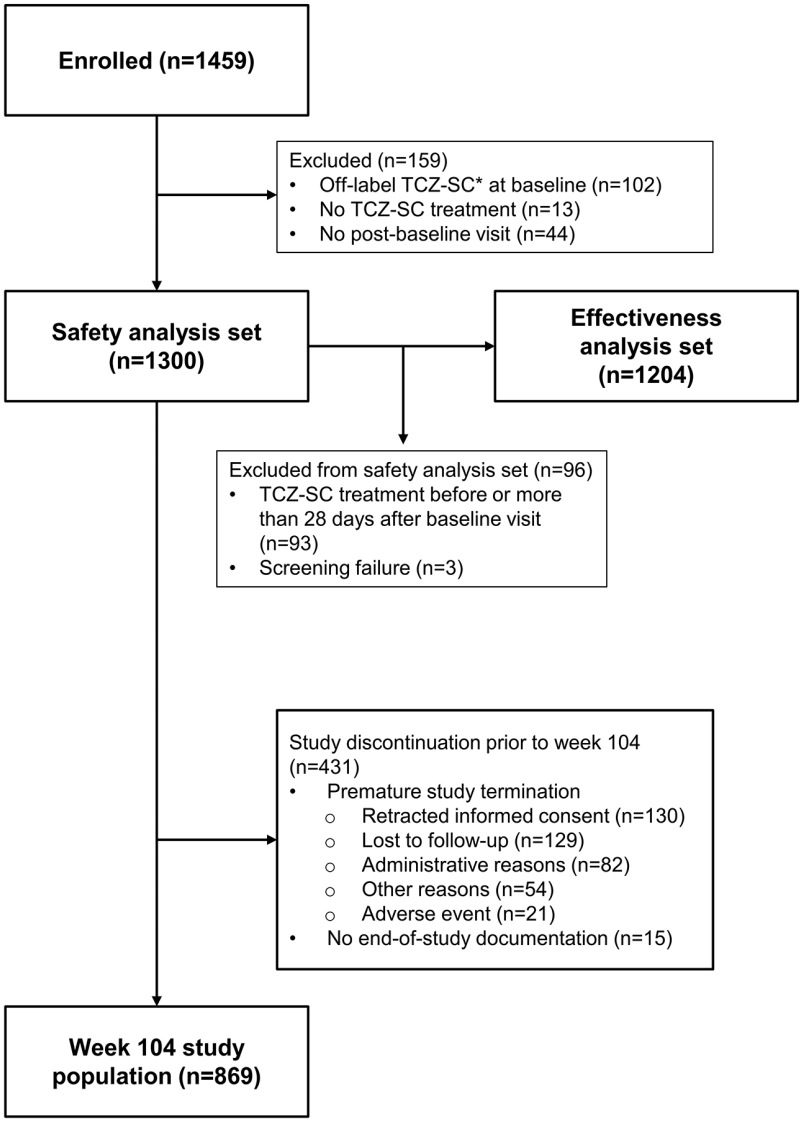

Fig. 1. Patient disposition.
*Off-label TCZ-SC treatment was defined as treatment with a csDMARD other than MTX (n=72) or no previous DMARD treatment (n=30).
csDMARD: conventional synthetic disease-modifying anti-rheumatic drug; DMARD: disease-modifying anti-rheumatic drug; MTX: methotrexate; TCZ-SC: subcutaneous tocilizumab.

Statistics

The target sample size was 1,500 patients from 150 to 200 centres (maximum of 80 patients per centre to ensure geographic diversity) based on an estimated DAS28-ESR remission rate of 57% for patients with previous biologic DMARD (bDMARD) therapy and 67% for bDMARD-naive patients. These rates were estimated on the basis of earlier, shorter-term studies with TCZ-IV and TCZ-SC (5, 6, 21-23),

since long-term data were not available at the time ARATA was designed.

Safety analyses were conducted on the safety analysis set, which included eligible patients who had received at least one dose of TCZ-SC at any time and had at least one post-baseline visit. Effectiveness analyses were conducted on the effectiveness analysis set, which consisted of all eligible patients who received the first dose of TCZ-SC on or within 4 weeks of the baseline visit and returned for at least one post-baseline visit.

Descriptive statistics or frequencies were computed for all data as appropriate. For all analyses except those involving time to DAS28-d_{crit} response (see below), missing data were not imputed.

Post hoc analyses were conducted on time to DAS28-d_{crit} response and Kaplan Meier analyses were used to evaluate whether baseline patient or disease characteristics influenced the time to response. All patients were included in the analyses. Patients without a DAS28-d_{crit} response were censored at time of last visit. The baseline parameters were chosen based on clinical guidance and included age, body mass index, disease duration, previous biologic treatment, FFbH, HAQ-DI, pain, fatigue, and WPAI scores. For all numerical variables, comparisons were made for the achievement of DAS28-d_{crit} in the subgroups with values below or above the cohort median. Analyses of the effect of previous biologic treatment compared achievement of DAS28-d_{crit} in biologic-experienced patients with response rates in biologic-naive patients.

Table I. Baseline characteristics and comorbidities.

Characteristic	n	Baseline value
Age, years, mean (SD)	1300	57.3 (12.5)
Female sex, n (%)	1300	971 (74.7)
RA disease duration, years, mean (SD)	1267	10.1 (9.2)
Disease activity measures, mean (SD)		
DAS28-ESR	954	4.9 (1.3)
CDAI	1129	25.1 (11.6)
CRP, mg/dL	709	2.3 (3.1)
ESR, mm/h	1060	28.5 (22.4)
Therapy immediately before study entry, n (%)		
sDMARD	1158	448 (38.7)
bDMARD	1158	623 (53.8)
Prior bDMARD therapy, n (%)		
bDMARD naive	1299	477 (36.7)
bDMARD experienced	1299	822 (63.3)
Concomitant sDMARD therapy, n (%)		
None (TCZ monotherapy)	1300	883 (67.9)
MTX	1300	417 (32.1)
Glucocorticoid therapy	1300	822 (63.2%)
Comorbidities, n (%)		
Any	1298	1034 (79.7)
Cardiovascular disease*	1034	622 (60.1)
Hypertension	1034	555 (53.7)
Musculoskeletal system disorders†	1032	615 (59.6)
Degenerative joint disease/disease of the spinal column	1032	405 (39.2)
Osteoporosis	1032	218 (21.1)
Metabolic disease	1034	373 (36.1)
Type II diabetes mellitus	1034	135 (13.1)
Hyperlipidaemia	1034	129 (12.5)
Central nervous system disorders§	1032	165 (16.0)
Respiratory disease	1032	115 (11.1)
Gastrointestinal disease	1032	104 (10.1)
Renal disease	1032	95 (9.2)

*Non-specified cardiovascular diseases included cardiac insufficiency, coronary heart disease, cerebrovascular disease (stroke, transient ischaemic attack, prolonged reversible ischaemic neurologic deficit), and other cardiovascular conditions.

†Non-specified musculoskeletal system disorders included fibromyalgia, crystalloarthropathy, spondyloarthritis, and others.

§Including depression, polyneuropathy, and other central nervous system disorders.

bDMARD: biologic disease-modifying antirheumatic drug; CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; DAS28: Disease Activity Score-28 joints; ESR: erythrocyte sedimentation rate; MTX: methotrexate; RA: rheumatoid arthritis; sDMARD: synthetic disease-modifying antirheumatic drug; SD: standard deviation; TCZ: tocilizumab.

Results

Patients and treatment

A total of 1,459 adult RA patients were enrolled at 114 study centres in Germany between May 2014 and July 2018. Of these patients, 1,300 were included in safety analyses and 1,204 were included in effectiveness analyses; the most common reason for study exclusion was the use of off-label TCZ-SC (in patients with no prior DMARD therapy or in combination with a csDMARD other than MTX) at baseline (Fig. 1). Among patients in the safety analysis set, the most common reason for exclusion from the efficacy analysis set was inappropriate timing of TCZ-SC initiation (prior to baseline or more than 4 weeks after the baseline visit) (n=93) (Fig. 1). A total of 869 patients (66.8% of the safety analysis set) completed the study. The major reasons for study discontinuation were retraction of informed consent and no follow-up data.

At baseline, patients in the study had a mean age of 57.3 years (standard deviation [SD] 12.5), moderate to high disease activity, as indicated by mean DAS28-ESR of 4.9 (SD 1.3), and a disease duration of approximately 10 years (Table I). Over half (53.8%) of the patients had been treated with another bDMARD, usually a TNF blocker, immediately prior to the switch to TCZ-SC. Most patients reported lack of effectiveness of their previous therapy as the reason for switching to TCZ-SC (1040/1300; 80.0%), followed by lack of tolerability (n=343; 26.4%) and other reasons (n=44; 3.4%) (multiple reasons could be listed). Comorbidities were common, particularly hypertension, musculoskeletal system disorders, and metabolic disease (Table I). At the baseline visit, 32.1% of TCZ-SC patients were prescribed con-

comitant MTX. Baseline demographic and disease characteristics were generally comparable between patients prescribed TCZ-SC + MTX and TCZ-SC monotherapy (DAS28 of 4.8 [SD 1.3] *vs*. 4.9 [SD 1.3]).

During the 2-year study, 383/1300 (29.5%) patients discontinued TCZ-SC (patients could discontinue TCZ-SC without discontinuing the study). The most common primary reason for discontinuing TCZ-SC (only one reason could be given) was an AE (205/1300; 15.8%) followed by worsening of disease (85/1300; 6.5%). Patients who were treated with TCZ-SC + MTX were more likely to discontinue treatment due to worsening of disease (39/417 [9.4%]) compared with patients on TCZ-SC monotherapy (46/883 [5.2%]). Of patients who remained in the study until week 104, 295/873 (33.8%) patients were not currently being treated with TCZ-SC. The mean duration of TCZ-SC treatment was 67.2 (SD 41.7) weeks.

Changes in disease activity over 2 years

Mean DAS28 decreased by approximately 50% in the overall study population during the course of the study, from a mean baseline score of 4.9 (SD 1.3) to 2.5 (SD 1.4) at week 104. Corresponding improvements were observed in DAS28 and CDAI remission and other response rates (Fig. 2). Of patients remaining in the study at week 104 with available data, 58.7% (365/622) and 31.4% (241/767) were in DAS28 and CDAI remission, respectively, and 72.7% (452/622) and 70.8% (543/767) had achieved LDA by DAS28 and CDAI, respectively. Remission and LDA rates were generally comparable regardless of concomitant MTX therapy and slightly higher in bDMARD-naive *versus* bDMARD-experienced patients, especially for CDAI remission (48.9% *vs*. 40.2%).

Analyses of individual therapeutic responses by use of the DAS28-d_{crit} criteria (improvement from baseline of ≥1.8) found that by week 4, 50% of patients with available data (n=607) had achieved an individual therapeutic response. DAS28-d_{crit} response rates increased to between 60% and 65% of the

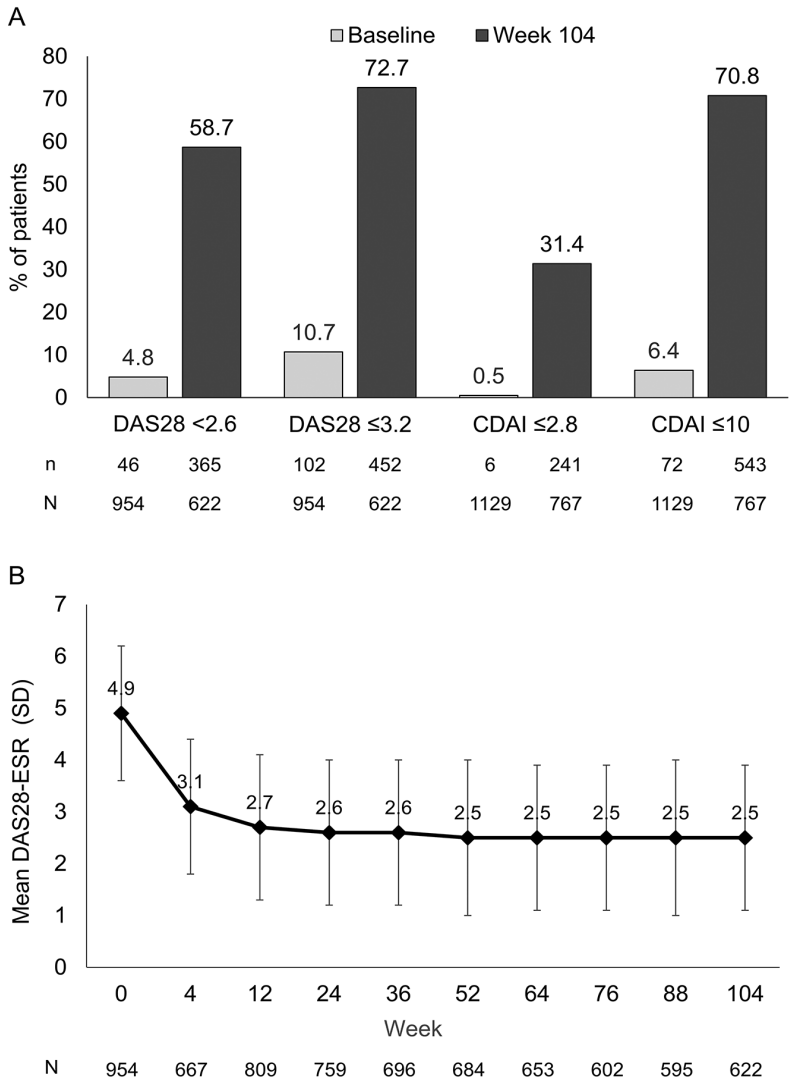

Fig. 2. Changes in disease activity during treatment with TCZ-SZ based on observed data in the effectiveness analysis set. **A**: Disease activity response rates at week 104; **B**: Mean (standard deviation) DAS28-ESR over time.

DAS28 <2.6 represents DAS28 remission; DAS28 ≤3.2 represents DAS28 LDA; CDAI ≤2.8 represents CDAI remission; CDAI ≤10 represents CDAI LDA. CDAI: Clinical Disease Activity Index; DAS28-ESR: Disease Activity Score based on 28 joints and erythrocyte sedimentation rate; LDA: low disease activity; SD: standard deviation; TCZ-SC: subcutaneous tocilizumab.

study cohort at subsequent timepoints; the week 104 response rate was 64.0% (n=547) (Fig. 3A). The median time to first DAS28-d_{crit} response was 85 days (range, 14–799 days) (Fig. 3B), and the median duration of response was 333 days (range, 1–1140 days) (Fig. 3C). The percentages of patients with DAS28-d_{crit} responses at week 104 were similar for females (252/400 [63.0%]) and males (98/147 [66.7%]) and generally robust across different age groups, with a slightly lower rate in patients >65 years of age (59.1% [75/127] compared with 64.2% [95/148] for ≤50 years and 66.2% [180/272] for >50 to ≤65 years).

Concomitant therapy with MTX had a negligible effect on DAS28-d_{crit} response rates at week 104 (64.9% [226/348] for TCZ-SC monotherapy *vs*. 62.3% [124/199] for TCZ-SC + MTX) or on time to response (Fig. 3B), but the duration of response was shorter in patients treated with concomitant MTX (median of 270 days [interquartile range (IQR) 99–624] *vs*. 345.5 days [IQR 118–637] for TCZ-SC monotherapy) (Fig. 3C). Patients who had received prior bDMARD therapy had lower response rates at week 104 (60.5% [228/377] for bDMARD-experienced *vs*. 71.8% [122/170] for

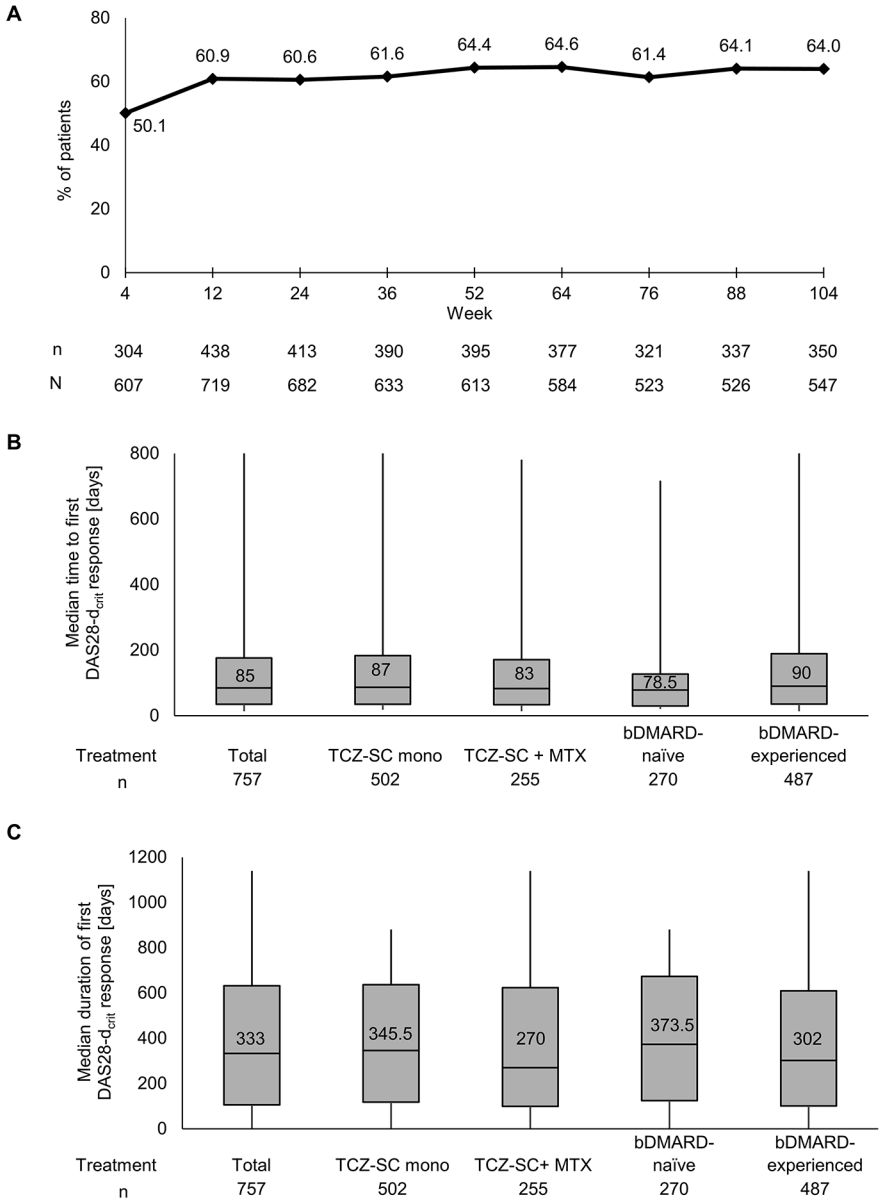

Fig. 3. DAS28-d_{crit} individual therapeutic responses in the effectiveness analysis set. **A**: Proportion of patients with DAS28-d_{crit} responses over time; **B**: median time to first DAS28-d_{crit} response; **C**: median duration of first DAS28-d_{crit} response. For B and C, boxes indicate median and interquartile range (Q1-Q3), and bars indicate minimum and maximum.
bDMARD: biologic disease-modifying anti-rheumatic drugs; DAS28: Disease Activity Score based on 28 joints; DAS28-d_{crit}: critical difference in DAS28 (improvement of ≥1.8 from baseline); mono: monotherapy; MTX: methotrexate; TCZ-SC: subcutaneous tocilizumab.

bDMARD-naive) (Supplementary Fig. S1), a longer time to DAS28-d_{crit} response (Fig. 3B), and a shorter duration of response (Fig. 3C).

Post-hoc time-to-event analyses did not reveal any associations between DAS28-d_{crit} responses and baseline characteristics, including age and previous biologic treatment.

Changes in PROs over 2 years

During the 104-week study, improvements were observed in PROs and WPAI assessments (Fig. 4). PtGA scores decreased by approximately 50% (from a mean of 63.5 [SD 21.6] at baseline to 29.6 [SD 24.9] at week 104), and strong reductions were also observed in pain and fatigue (Fig. 4A). Sleep disturbance had the lowest level of improvement. Functional assessments showed more modest improvements: HAQ-DI improved from 1.2 (SD 0.7) at baseline (n=1,020) to 0.9 (SD 0.7) at week 104 (n=624), while FFbH improved from 63.5 (SD 22.8) at baseline (n=1,050) to 70.7 (SD 22.8) at week 104 (n=644).

All WPAI assessments indicated improvements in work productivity during the study (Fig. 4B). In particular, absenteeism scores decreased from a mean of 20.4 (SD 34.1) at baseline to 9.3 (SD 22.4) at week 104 and mean presenteeism scores improved from 54.8 (SD 28.4) at baseline to 29.3 (SD 25.5) at week 104.

Safety

The AEs reported during this study were consistent with previous TCZ studies and no unexpected AEs were observed. Over the 104-week study, 13/1300 patients (1.0%) experienced an injection site reaction and 301 (23.2%) discontinued TCZ-SC due at least in part to any AE (as might be expected, this number is higher than the number who listed AEs as a primary reason for discontinuation [n=205]). Forty-five patients (3.5%) experienced an SAE considered by the investigator to be related to TCZ (Table II). The most common AE by SOC was infections and infestations (22.5%). IV anti-infectives were required by 102 (7.8%) patients. Medically significant hepatic events occurred in 37 (2.8%) of patients and anaphylaxis in 17 (1.3%). No other AEs of special interest occurred in more than 1% of patients. Eleven patients died; causes of death are presented in the Table II legend.

Compared with the TCZ monotherapy subgroup, the TCZ + MTX subgroup had slightly higher AE rates (479/883 [54.2%] *vs*. 259/417 [62.1%]) and SAE rates (130/883 [14.7%] *vs*. 72/417 [17.3%]), but differences were small.

Patient satisfaction

At post-baseline visits, from 76% to 89% of patients expressed satisfaction with TCZ-SC throughout the study, 75% to 83% did not feel restricted by TCZ-SC, and 57% to 80% would recommend TCZ-SC to other patients (Supplementary Fig. S2). Patient opinion ratings tended to improve during the study and the highest ratings were recorded at the final visit (week 104).

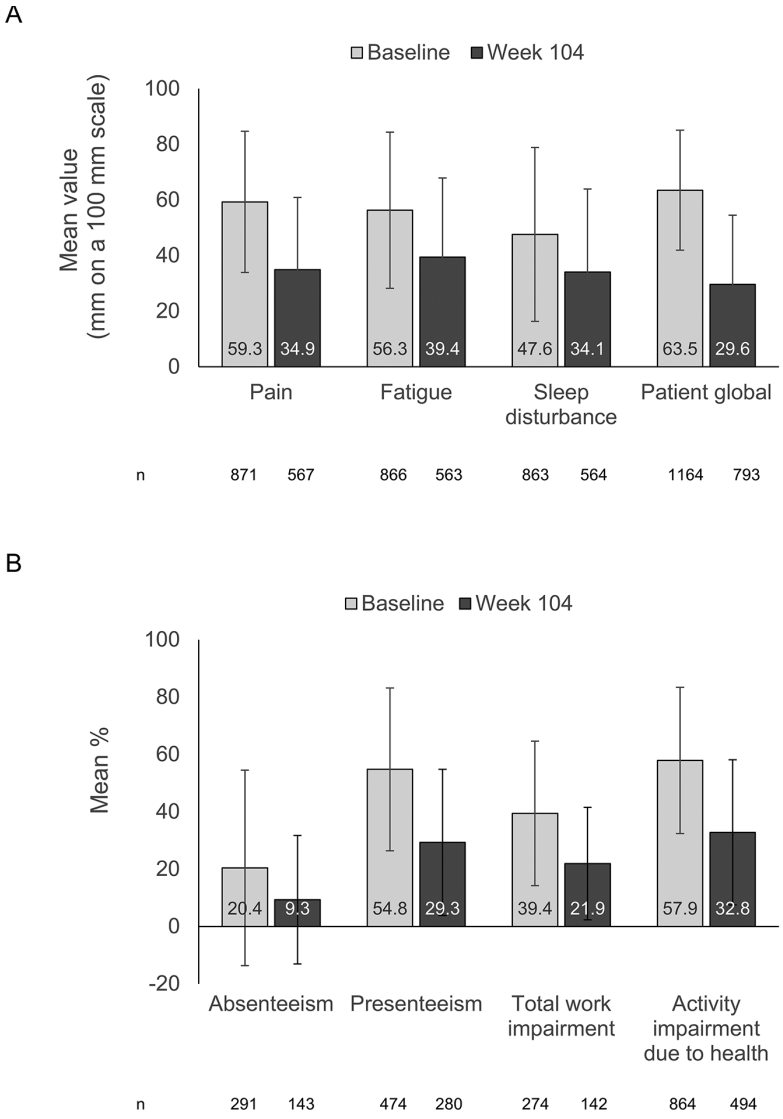

Fig. 4. (**A**) Patient-reported outcomes and (**B**) WPAI assessments at baseline and week 104 in the effectiveness analysis set. Bars indicate mean values and lines represent standard deviations.
For patient outcomes, data are reported as mm on a 100-mm visual analogue scale. Lower scores indicate improved status. For all WPAI assessments, patients were asked to provide estimates over the last 7 days. WPAI absenteeism = % of missed work hours; WPAI presenteeism = % of impairment at work; total work impairment = % overall work impairment; and activity impairment due to health = % of impairment attributed to health. WPAI: Work Productivity and Activity Impairment.

Patients generally rated the pain associated with TCZ-SC administration as low and consistent over the two-year time period. Mean pain ratings on a scale of 0 (no pain) to 10 (extreme pain) were 2.2 (SD 2.2) at baseline and 2.2 (SD 2.0) at week 104.

Comparison between the ARATA and ICHIBAN studies

We compared key baseline characteristics and week 104 outcomes for TCZ-SC in the ARATA study (2014 to 2018) and TCZ-IV in the ICHIBAN study (2010 to 2017) (11) to see whether patient populations or outcomes varied based on TCZ formulation or the different years during which the studies were conducted. Despite these differences between the studies, both baseline characteristics and outcomes at week 104 were remarkably similar (Supplementary Table S1). For instance, DAS28-ESR over time decreased from a baseline value of 4.9 (SD 1.3) to 2.5 (SD 1.4) at week 104 in the ARATA study compared with reductions from a baseline value of 5.0 (SD 1.5) to 2.3 (SD 1.4) at week 104 in the ICHIBAN study.

Discussion

In this study of RA patients under routine care, TCZ-SC demonstrated sustained effectiveness and safety over 2 years in patients remaining on therapy. DAS28-ESR remission was achieved by over half (58.7%) of patients at week 104 and CDAI remission was achieved by almost one-third (31.4%). Previous studies of both TCZ (11) and other biologic and non-biologic DMARDs (24, 25) have also noted higher remission rates with DAS28-ESR compared with CDAI, likely due to the lower contribution of joint counts and impact of an acute phase reactant in DAS28 values (24, 25).

Assessments of individual therapeutic responses found that 64% of patients had a DAS28-d_{crit} response, defined as a DAS28-ESR reduction of ≥1.8 from baseline, at week 104. DAS28-dcrit responses were sustained for a median of slightly less than 1 year, consistent with other reports documenting the stability of DAS28-d_{crit} responses (16, 26). Time-to-event and Kaplan-Meier analyses did not identify any significant associations between baseline characteristics and DAS28-d_{crit} responses. This absence of associated baseline characteristics suggests that the benefits of TCZ-SC treatment extend across a wide range of patients and are not limited by age, body mass index, or previous treatment. A shorter duration of response was observed in patients treated with TCZ + MTX, perhaps suggesting more aggressive disease in these patients. In support of this hypothesis, this subgroup also had a higher rate of discontinuation due to worsening disease.

PROs, including pain, fatigue, and sleep disturbance, play a major role in patients' perceptions of well-being; discrepancies in assessment of these facets of disease activity explain a large proportion of discordance between physician and patient evaluations (27, 28). PtGA, pain, fatigue, and sleep disturbance improved during TCZ treatment. At the population level, these changes exceeded the minimum clinically important difference (MCID) reported for PtGA (18-point MCID (29) *vs*. 33.9-point change from baseline in mean score), pain (20-point MCID (29)

Table II. Adverse event rates in the safety analysis set (n=1300).

Adverse event	Number of events	Number of patients (%)
Any	1966	738 (56.8)
Injection site reactions	19	13 (1.0)
Discontinuation of TCZ-SC due to AE	390	301 (23.2)
SAEs	324	202 (15.5)
SAEs related to TCZ-SC	58	45 (3.5)
Serious infections	61	50 (3.8)
AEs resulting in death*	15	11 (0.8)
AEs occurring in ≥5% of patients by SOC		
Infections and infestations	503	292 (22.5)
General disorders and administration site conditions	290	221 (17.0)
Musculoskeletal and connective tissue disorders	226	167 (12.8)
Skin and subcutaneous tissue disorders	142	119 (9.2)
Gastrointestinal disorders	143	117 (9.0)
Nervous system disorders	95	82 (6.3)
Investigations	106	75 (5.8)
AEs of special interest	226	184 (14.2)
Infections†	131	102 (7.8)
Medically significant hepatic event	41	37 (2.8)
Anaphylaxis	18	17 (1.3)
Malignancies	13	13 (1.0)
Bleeding events	10	9 (0.7)
MI/acute coronary syndrome	8	8 (0.6)
GI perforation and related events	3	3 (0.2)
Demyelination events	1	1 (0.1)
Stroke	1	1 (0.1)

*Specific causes of death were: multiorgan failure associated with recurrent *S. aureus* infection (n=1), renal failure (n=1), renal and liver failure (n=1), carcinoma with metastases in lung and liver (n=1), sepsis (n=1), cardiovascular failure with brain compression and sepsis (n=1), and unknown (n=5).
†Including opportunistic infections and events treated with IV anti-infectives.
AE: adverse event; GI: gastrointestinal; MI: myocardial infarction; SAE: serious adverse event; SOC: system organ class; TCZ-SC: subcutaneous tocilizumab.

vs. 24.4-point change from baseline in mean score), and fatigue (10-point MCID (30) *vs*. 16.9-point change from baseline in mean scores). More modest improvements were reported in physical function, likely due to the relatively long RA disease duration (mean of 10.1 years), which is known to impact HAQ-DI changes (31). Nevertheless, the mean population change from baseline in HAQ-DI was 0.3 in our study, which exceeds the MCID for HAQ-DI based on the frequently-used criterion of 0.22 (32). In addition to the PROs reported here, a previous analysis of ARATA data found that depressive symptoms, as assessed by Beck Depression Inventory II (BDI-II) scores, also improved over 52 weeks, and BDI-II improvements appeared to be distinct from changes in disease activity (33). Together, these findings support the favourable impact of TCZ on RA symptoms as experienced by patients.

For patients with RA, absence from work (absenteeism) and lower productivity while at work (presenteeism) contribute to reduced work productivity (34), which is associated with substantial societal and individual costs (35) and reduced quality of life (36). During TCZ-SC therapy, both absenteeism and presenteeism improved, as did total work impairment and work impairment due to health. For all WPAI outcomes, the magnitude of improvement in mean values was greater than the MCID of 7% (37, 38), indicating that TCZ-SC therapy was associated with meaningful improvements. It should be noted, however, that standard deviations were large and respondent numbers were low for some outcomes.

Our WPAI findings are consistent with a study reporting improved work outcomes with TCZ-SC compared with DMARDs in a Japanese RA population (39).

Safety analyses showed low rates of injection site reactions (1.0%) and no unexpected safety signals. Serious infections were observed in 3.8% of patients over the 2-year study; this rate is similar to the 3.95% rate of serious infections with TCZ-SC reported at 97 weeks in the randomised SUMMACTA trial (6).

Despite the different formulations and time periods for the ARATA study and the previously-reported ICHIBAN observational study of TCZ-IV at German rheumatology centres (11), both baseline characteristics and effectiveness outcomes were similar in these studies. An analysis of data from the Tocilizumab Collaboration of European Registries in RA also reported similar effectiveness and retention for TCZ-SC and TCZ-IV (40). These findings provide further support for the comparability of the two formulations during routine daily care, thereby allowing clinicians to tailor TCZ treatment choice based on patient preference.

Study limitations are those inherent to observational studies, including the absence of a control arm, missing data for some assessments, and the potential for underreporting safety data. As this was not a randomised study, potential channeling bias by clinicians (*e.g*. opting for TCZ-SC over other therapies on the basis of patient characteristics such as severity of illness or comorbidities) could have potentially influenced cohort composition and outcomes. Although investigators were allowed to include radiographic and ultrasound data on the online case report form, post-baseline data were entered very rarely and therefore an evaluation of the effect of TCZ-SC on radiographic progression or ultrasound scores was not statistically meaningful. Results at later time points were likely influenced by responder bias, in which patients with a good response or greater treatment satisfaction are more likely to stay in the study. We tried to diminish this by choosing a study design in which patients could discontinue TCZ-SC but continue in the study. About one-third of patients remaining in the study at week 104 were not taking TCZ-SC, which may have resulted in

over- or under-estimates of long-term outcomes.

In conclusion, we found that TCZ-SC is safe and effective for over 2 years in patients with RA treated in routine daily care. TCZ-SC provides a convenient treatment option for patients with RA who may benefit from IL-6 receptor inhibition and prefer a therapy that can be self-administered.

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Competing interests

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