

# Treatment of Rheumatoid Arthritis With Anti-Tumor Necrosis Factor or Tocilizumab Therapy as First Biologic Agent in a Global Comparative Observational Study

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**Objective.** To compare clinical effectiveness between tocilizumab and tumor necrosis factor inhibitors (TNFi) in patients with rheumatoid arthritis (RA) and inadequate response to conventional synthetic disease-modifying antirheumatic drugs initiating biologic therapy.

**Methods.** Patients prescribed tocilizumab (intravenous) or TNFi were prospectively observed in routine clinical practice for 52 weeks across 158 sites in 26 countries. The primary observation was the change from baseline in Disease Activity Score based on 28 joints using the erythrocyte sedimentation rate (DAS28-ESR) at week 24 using analysis of covariance for between-groups comparison. Secondary end points included Clinical Disease Activity Index (CDAI) and patient-reported outcomes at weeks 24 and 52.

**Results.** Of 1,216 patients, 35% initiated tocilizumab and 65% initiated TNFi. RA duration was shorter, and disease activity and corticosteroid use were higher in tocilizumab patients. Tocilizumab-treated patients had greater improvement in DAS28-ESR at weeks 24 and 52 (week 24 difference [95% confidence interval] in adjusted means:  $-0.831 [-1.086, -0.576]$ ;  $P < 0.001$ ). Change from baseline in CDAI was also greater with tocilizumab (adjusted means difference: week 24,  $-3.48$ ; week 52,  $-4.60$ ; both  $P < 0.001$ ). Tocilizumab-treated patients had more improvement in the Health Assessment Questionnaire disability index than TNFi-treated patients ( $P < 0.05$ ). The cumulative probability of drug discontinuation at week 52 was lower with tocilizumab (15%) than TNFi (27%;  $P < 0.001$ , unadjusted analysis). Unadjusted frequencies (events per 100 patient-years) for tocilizumab and TNFi were 6.44 and 11.99 for serious adverse events, 1.98 and 5.03 for serious infections, and 0.74 and 0.77 for deaths, respectively.

**Conclusion.** Patients initiating tocilizumab experienced greater effectiveness and drug survival than those initiating TNFi in an observational setting.

## INTRODUCTION

Current American College of Rheumatology (ACR) and European League Against Rheumatism guidelines recommend initiating treatment with biologic disease-modifying

antirheumatic drugs (DMARDs) in patients with rheumatoid arthritis (RA) who have not responded to conventional synthetic DMARDs (csDMARDs) or who have high disease activity and features of poor prognosis (1,2). Many biologic agents are available for the treatment of RA; tumor necrosis

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## Significance & Innovations

- To date, comparative efficacy of the interleukin-6 receptor  $\alpha$  monoclonal antibody tocilizumab (TCZ) and tumor necrosis factor inhibitors (TNFi) for the treatment of rheumatoid arthritis has been investigated in a single head-to-head trial of TCZ monotherapy versus adalimumab monotherapy and network meta-analyses.
- This prospective, observational, comparative effectiveness study provides the first real-world evidence of effectiveness and persistence on treatment for patients who initiated TCZ compared with those who initiated TNFi in routine clinical practice, as measured by the Disease Activity Score in 28 joints using the erythrocyte sedimentation rate and the Clinical Disease Activity Index.

factor inhibitors (TNFi), abatacept, and the interleukin-6 (IL-6) receptor  $\alpha$  inhibitor tocilizumab are recommended; under certain circumstances, rituximab may be used (2). However, evidence is lacking regarding which biologic agents should be used and in what sequence.

Only a few head-to-head clinical trials comparing biologic agents in patients with RA have been conducted to date. The randomized controlled phase IV ADACTA trial in patients with RA who were intolerant of methotrexate or for whom continued therapy with methotrexate was inappropriate demonstrated superiority of tocilizumab monotherapy over adalimumab monotherapy for change in the Disease Activity Score in 28 joints using the erythrocyte sedimentation rate (DAS28-ESR) from baseline to week 24. More tocilizumab-treated than adalimumab-treated patients achieved remission according to the DAS28-ESR (DAS28 <2.6) and the Clinical Disease Activity Index (CDAI  $\leq$ 2.8) (3). The phase IIIb AMPLE (Abatacept versus Adalimumab Comparison in Biologic-Naive RA Subjects with Background Methotrexate) trial demonstrated similar clinical efficacy and inhibition of radiographic progression between abatacept and adalimumab in combination with methotrexate in patients with RA who had an inadequate response to methotrexate (4). Rituximab was noninferior to TNFi treatment for change in the DAS28-ESR in the open-label ORBIT (Optimal Management of RA Patients Who Require Biologic Therapy) trial in patients with RA who had an inadequate response to csDMARDs (5). Comparison of effectiveness and drug survival between tocilizumab and TNFi in RA is limited to indirect comparison of clinical trial data and small observational studies (6–9).

The current study (ACT-iON) is the first prospective, large-scale, global, multicenter, comparative effectiveness study comparing initiation of intravenous tocilizumab with initiation of a TNFi in patients with RA as the first-line biologic agent treatment after an inadequate response to csDMARDs in a real-world, clinical practice setting. Biologic therapy may be initiated in combination with csDMARDs or as monotherapy in clinical practice according to the decision of the treating physician; this study provides an opportunity to

compare tocilizumab and TNFi therapy in combination with csDMARDs.

## PATIENTS AND METHODS

**Study design.** ACT-iON was conducted at 158 sites in 26 countries (ClinicalTrials.gov: NCT01543503). Clinical effectiveness and safety outcomes of TNFi and tocilizumab were observed for 52 weeks of routine clinical practice after the initiation of the first biologic-agent therapy for the treatment of patients with RA. The study was observational; no additional diagnostic or therapeutic procedures were performed beyond routine clinical practice.

**Patients.** The study included adult patients with moderate to severe RA, defined according to 1987 ACR criteria (10), of at least 24 weeks' duration who were nonresponders or who were intolerant of csDMARD therapy and whose treating physicians decided to initiate treatment with a TNFi or with intravenous tocilizumab in accordance with the local label (tocilizumab was initiated at 8 mg/kg in all patients because the study was not conducted in the US or Canada, where the starting dose is 4 mg/kg [11,12]) as their first biologic agent. The study was conducted in compliance with the Declaration of Helsinki and Good Clinical Practice and with the institutional review board/ethics committee. Patients provided written informed consent.

**Assessments.** Data were collected between February 9, 2012 and February 20, 2015. Patients might have initiated treatment before study start because the enrollment visit could occur up to 6 weeks after initiation of the first biologic agent. The primary observation was the mean change from baseline in the DAS28-ESR at week 24. Secondary outcome measures included mean change from baseline in the DAS28-ESR at week 52, swollen joint count (SJC), tender joint count (TJC), remission rates according to the DAS28-ESR and CDAI, and patient-reported outcomes, including the Health Assessment Questionnaire disability index (HAQ DI). Safety was assessed throughout the study by monitoring adverse events (AEs), serious AEs (SAEs), abnormalities in laboratory assessments, and vital signs.

**Statistical analysis.** The initial target sample size was 2,000 patients, which was expected to provide 90% power to detect a between-groups difference of 0.3 DAS28 units. However, a slower than anticipated recruitment rate resulted in a final sample size of 1,225 patients, which was expected to provide a detectable difference of approximately 0.4 DAS28 units. Safety was assessed in the safety population (all patients who received  $\geq$ 1 dose of a TNFi or tocilizumab). The primary effectiveness analysis population included all patients in the safety population administered their first biologic agent within 60 days after the previous RA disease activity measurement.

Missing values were not imputed for the primary analyses. Significance was determined as a *P* value less than 0.05 without correction for multiple testing. Differences in baseline characteristics were assessed using the Wilcoxon rank sum test or chi-square test. Estimation of the primary outcome in the 2 treatment groups was based on an analysis of

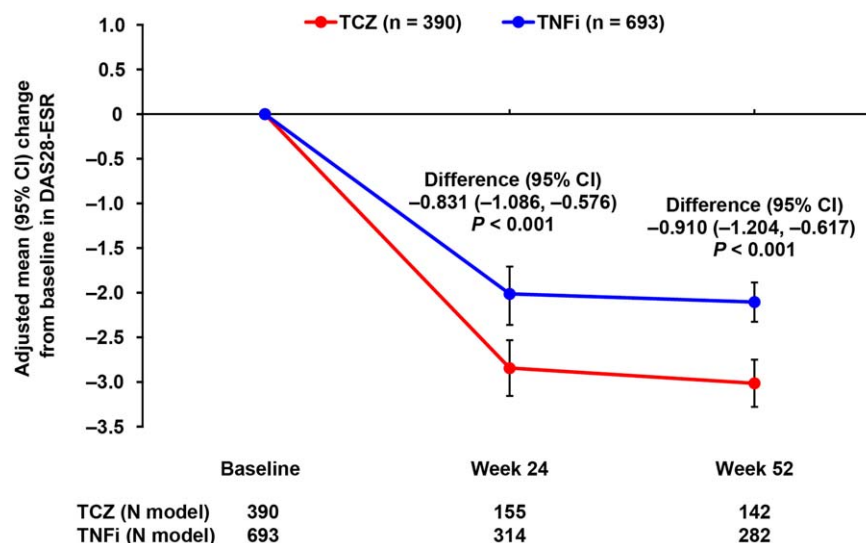
**Table 1. Baseline demographics and treatments (safety population—all patients)\***

	TCZ (n = 423)	TNFi (n = 793)	P
Age, mean ± SD years	54.3 ± 12.8	55.2 ± 13.1	0.171†
Disease duration, mean ± SD years	7.8 ± 7.3	9.4 ± 9.0	0.014†
DAS28-ESR, mean ± SD‡	5.8 ± 1.1§	5.5 ± 1.2¶	0.030†
SJC, mean ± SD‡	9.0 ± 6.2#	7.4 ± 5.3**	< 0.001†
TJC, mean ± SD‡	12.1 ± 6.9††	12.1 ± 7.6**	0.688†
CDAI, mean ± SD‡	33.0 ± 13.5‡‡	31.2 ± 13.2§§	0.077†
HAQ DI, mean ± SD‡	1.5 (0.7)§	1.5 (0.7)¶¶	0.968†
Initiated biologic agent as monotherapy, no. (%)	119 (28.1)	127 (16.0)	< 0.001##
Initiated biologic agent in combination with csDMARDs, no. (%)	312 (73.8)	679 (85.6)	–
MTX, no. (%) [median dose, mg/week]***	233 (74.7) [15.0]	541 (79.7) [15.0]	–
Hydroxychloroquine, no. (%)†††	70 (22.4)	179 (26.4)	–
Leflunomide, no. (%)†††	73 (23.4)	124 (18.3)	–
Sulfasalazine, no. (%)†††	37 (11.9)	122 (18.0)	–
Oral corticosteroid use, no. (%)‡‡‡	256 (60.5)	369 (46.5)	< 0.001##
Oral corticosteroid dose, mean ± SD mg/day‡‡‡	8.3 (5.55)§§§	7.3 (5.31)§§	–
History of comorbid conditions, no. (%)			
Other autoimmune disease	32 (7.6)	41 (5.2)	0.205¶¶¶
Overlap syndrome	10 (2.4)	12 (1.5)	0.060¶¶¶
Chronic hepatic impairment	11 (2.6)	27 (3.4)	0.774¶¶¶
Severe and/or progressive infection	12 (2.8)	22 (2.8)	0.709¶¶¶
Central nervous system demyelination	5 (1.2)	3 (0.4)	0.178¶¶¶
Severe immunosuppression	0 (0.0)	2 (0.3)	0.518¶¶¶
Malignant tumor	20 (4.7)	12 (1.5)	0.005¶¶¶
Lymphoproliferative syndrome	1 (0.2)	0 (0.0)	0.016¶¶¶
Angina/other heart disease	51 (12.1)	120 (15.1)	0.327¶¶¶
Other clinically significant comorbidities	258 (61.0)	512 (64.6)	0.451¶¶¶

\* TCZ = tocilizumab; TNFi = tumor necrosis factor inhibitor; DAS28-ESR = Disease Activity Score in 28 joints using the erythrocyte sedimentation rate; SJC = swollen joint count; TJC = tender joint count; CDAI = Clinical Disease Activity Index; HAQ DI = Health Assessment Questionnaire disability index; csDMARDs = conventional synthetic disease-modifying antirheumatic drugs; MTX = methotrexate.  
† Based on Wilcoxon's rank sum test.  
‡ Primary effectiveness population.  
§ N = 230.  
¶ N = 402.  
# N = 352.  
\*\* N = 621.  
†† N = 353.  
‡‡ N = 238.  
§§ N = 358.  
¶¶ N = 408.  
## Based on chi-square test for comparison of monotherapy and combination therapy between both treatment groups.  
\*\*\* Percentages based on number of patients who initiated a biologic agent in combination with csDMARDs. For MTX dose: TCZ, n = 233; TNFi, n = 538.  
††† Percentages based on number of patients who initiated biologic agent in combination with csDMARDs.  
‡‡‡ Prednisone equivalent.  
§§§ N = 248.  
¶¶¶ Based on Fisher's exact test.

covariance (ANCOVA) model that included baseline DAS28-ESR as a covariate and concomitant csDMARDs and country as factors. Given the selection and channeling bias possible in observational studies (13,14), supportive analyses were performed for DAS28-ESR and CDAI change from baseline to week 24 using matched-pair analysis based on the propensity score. This was computed using multiple logistic regression based on all relevant and evaluable baseline covariates (see Supplementary Table 1, available on the *Arthritis Care & Research* web site at <http://onlinelibrary.wiley.com/doi/10.1002/acr.23303/abstract>). Post hoc sensitivity analyses were performed on the primary end point using any type of DAS28 to account for missing DAS28-ESR

values. Data were restricted to patients with baseline disease activity assessments within 0–14 days before their first biologic agent treatment and used multiple imputation of missing week 24 DAS28-ESR values in the same ANCOVA model as that for the primary analysis. Additional post hoc sensitivity analyses included adjustment for age, disease duration, seropositivity, steroid use at baseline, history of malignant tumor, and treatment in the ANCOVA model. Models similar to those for the primary analysis were used to analyze other end points, such as CDAI and joint counts. Chi-square analysis was used for between-groups comparisons of the proportion of patients in DAS28 remission and other categorical variables. Drug survival was analyzed



**Figure 1.** Adjusted mean change from baseline to weeks 24 (primary end point) and 52 in the Disease Activity Score in 28 joints using the erythrocyte sedimentation rate (DAS28-ESR; primary effectiveness population—all patients). Analyses were based on analysis of covariance models, with changes from baseline in DAS28-ESR at week 24 or 52 as dependent variables, country (week 24 analysis) and treatment as fixed effects, and DAS28-ESR at baseline as a covariate. 95% CI = 95% confidence interval; TCZ = tocilizumab; TNFi = tumor necrosis factor inhibitor.

according to the Kaplan-Meier method, and between-groups comparisons were performed based on the log rank test.

## RESULTS

**Patient disposition.** In total, 1,216 patients initiated tocilizumab or TNFi therapy as their first biologic agent. Tocilizumab was initiated in 423 patients (35%) and TNFi in 793 patients (65%). The safety population was composed of the same 423 patients treated with tocilizumab and 793 patients treated with TNFi. The primary effectiveness population included 390 patients treated with tocilizumab and 693 patients treated with TNFi (see Supplementary Figure 1 and Supplementary Table 2, available on the *Arthritis Care & Research* web site at <http://onlinelibrary.wiley.com/doi/10.1002/acr.23303/abstract>). Of the TNFi-treated patients, 315 (39.7%) received etanercept, 203 (25.6%) received adalimumab, 155 (19.5%) received certolizumab pegol, 65 (8.2%) received infliximab, and 55 (6.9%) received golimumab. Excluding 21 screen failures, 162 patients (13.3%) withdrew from the study overall: 75 (17.7%) among patients who initiated tocilizumab as a first biologic drug and 87 (11.0%) among patients who initiated TNFi. The most common reason was loss to followup, which occurred for 32 tocilizumab-treated patients (7.6%) and 36 TNFi-treated patients (4.5%). Nine tocilizumab-treated patients (2.1%) and 13 TNFi-treated patients (1.6%) withdrew because of AEs, 4 tocilizumab-treated (0.9%) and 16 TNFi-treated patients (2.0%) withdrew because of lack of efficacy, and 8 tocilizumab-treated (1.9%) and 10 TNFi-treated patients (1.3%) withdrew consent. Overall, 34 patients (2.8%) withdrew for other reasons; 22 (5.2%) of them received tocilizumab and 12 (1.5%) received TNFi.

Tocilizumab was initiated more often than TNFi as monotherapy (28.1% versus 16.0%;  $P < 0.001$ ) (Table 1).

**Baseline characteristics.** Baseline demographics, disease characteristics, and concomitant therapies were only partially similar between the groups. Patients initiating tocilizumab had shorter mean  $\pm$  SD disease duration than patients who initiated TNFi ( $7.8 \pm 7.3$  years versus  $9.4 \pm 9.0$  years;  $P = 0.014$ ). They also had a slightly higher mean  $\pm$  SD DAS28-ESR ( $5.8 \pm 1.1$  versus  $5.5 \pm 1.2$ ;  $P = 0.030$ ) and SJC ( $9.0 \pm 6.2$  versus  $7.4 \pm 5.3$ ;  $P < 0.001$ ) and more frequent oral corticosteroid use (60.5% versus 46.5%;  $P < 0.001$ ) than patients who started TNFi. Among combination therapy patients, the most common concomitant csDMARD at baseline was methotrexate (74.7% for tocilizumab-treated patients and 79.7% for TNFi-treated patients); in both groups, the median dosage was 15 mg/week (Table 1). Additional baseline characteristics are shown in Supplementary Table 3, available on the *Arthritis Care & Research* web site at <http://onlinelibrary.wiley.com/doi/10.1002/acr.23303/abstract>.

Significant effects associated with the treatment choice were country (UK and Spain were countries with clearly larger proportions of patients receiving TNFi), and intolerance was a reason for stopping the previous csDMARD (favoring the choice of tocilizumab: odds ratio [OR] 0.59 [95% confidence interval (95% CI) 0.42, 0.82],  $P = 0.002$ ) and current alcohol intake (favoring TNFi: OR 1.83 [95% CI 1.16, 2.88],  $P = 0.0092$ ) (see Supplementary Table 1, available on the *Arthritis Care & Research* web site at <http://onlinelibrary.wiley.com/doi/10.1002/acr.23303/abstract>).

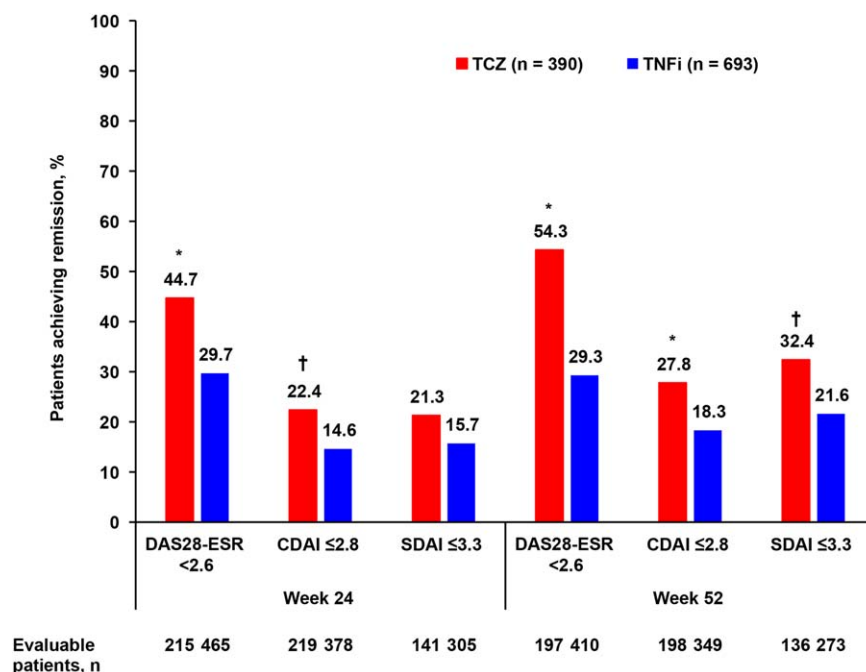
**Effectiveness.** Patients who received tocilizumab as their first biologic agent had significantly more change from baseline in DAS28-ESR to week 24 (primary end point) and week

**Table 2. Adjusted mean change from baseline to weeks 24 and 52 in secondary end points (primary effectiveness population—all patients)\***

	Week 24				Week 52			
	TCZ (n = 390)	TNFi (n = 693)	Difference (95% CI)	P	TCZ (n = 390)	TNFi (n = 693)	Difference (95% CI)	P
	ESR	-22.73 (-24.72, -20.75) n = 225	-9.50 (-11.11, -7.89) n = 456	-13.23 (-15.51, -10.95)	< 0.001	-21.52 (-23.88, -19.16) n = 215	-8.87 (-10.87, -6.87) n = 411	-12.65 (-15.42, -9.88)
CRP	-11.01 (-14.13, -7.88) n = 177	-4.33 (-6.86, -1.81) n = 396	-6.67 (-10.27, -3.07)	< 0.001	-6.33 (-10.52, -2.14) n = 173	-5.22 (-8.71, -1.72) n = 348	-1.12 (-6.07, 3.84)	0.66
SJC	-5.70 (-6.12, -5.27) n = 288	-5.12 (-5.48, -4.76) n = 554	-0.58 (-1.08, -0.08)	0.024	-6.31 (-6.72, -5.90) n = 258	-5.56 (-5.91, -5.21) n = 503	-0.75 (-1.24, -0.27)	0.002
TJC	-7.92 (-8.59, -7.25) n = 289	-7.30 (-7.87, -6.74) n = 554	-0.62 (-1.41, 0.17)	0.123	-8.42 (-9.12, -7.72) n = 259	-7.21 (-7.80, -6.61) n = 501	-1.22 (-2.04, -0.39)	0.004
CDAI	-20.25 (-21.93, -18.57) n = 176	-16.78 (-18.28, -15.27) n = 286	-3.48 (-5.48, -1.47)	< 0.001	-22.85 (-24.63, -21.06) n = 162	-18.25 (-19.82, -16.67) n = 267	-4.60 (-6.71, -2.49)	< 0.001
SDAI	-21.39 (-23.67, -19.12) n = 93	-18.16 (-20.05, -16.28) n = 193	-3.23 (-5.81, -0.65)	0.014	-22.29 (-24.79, -19.80) n = 91	-19.05 (-21.13, -16.97) n = 169	-3.25 (-6.12, -0.37)	0.027
HAQ DI	-0.59 (-0.69, -0.49) n = 169	-0.45 (-0.54, -0.35) n = 301	-0.15 (-0.27, -0.02)	0.020	-0.59 (-0.71, -0.48) n = 152	-0.43 (-0.54, -0.32) n = 255	-0.16 (-0.30, -0.03)	0.020
FACIT fatigue	-7.15 (-10.00, -4.30) n = 64	-3.26 (-6.28, -0.24) n = 86	-3.89 (-7.46, -0.33)	0.032	-4.57 (-7.82, -1.31) n = 50	-1.78 (-5.10, 1.54) n = 77	-2.79 (-6.76, 1.19)	0.168
Pain VAS	-29.31 (-32.92, -25.69) n = 204	-23.65 (-26.66, -20.63) n = 378	-5.66 (-9.91, -1.41)	0.009	-32.96 (-36.71, -29.20) n = 183	-23.16 (-26.39, -19.92) n = 336	-9.80 (-14.25, -5.36)	< 0.001

\* Data are adjusted means (95% confidence interval [95% CI]) unless indicated otherwise. N values are the number of evaluable patients included in the analysis of covariance model. TCZ = tocilizumab; TNFi = tumor necrosis factor inhibitor; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; SJC = swollen joint count; TJC = tender joint count; CDAI = Clinical Disease Activity Index; SDAI = Simplified Disease Activity Index; HAQ DI = Health Assessment Questionnaire disability index; FACIT = Functional Assessment of Chronic Illness Therapy; VAS = visual analog scale.





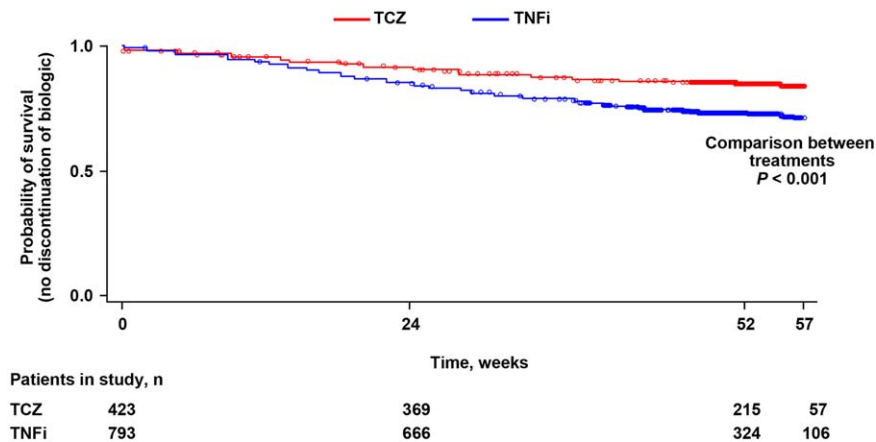
**Figure 2.** Proportions of patients achieving remission at weeks 24 and 52 according to the Disease Activity Score in 28 joints using the erythrocyte sedimentation rate (DAS28-ESR), the Clinical Disease Activity Index (CDAI), and the Simplified Disease Activity Index (SDAI) criteria (primary effectiveness population—all patients; unadjusted analysis). \* =  $P < 0.001$  and † =  $P < 0.05$  for tocilizumab (TCZ) vs. tumor necrosis factor inhibitor (TNFi; chi-square test).

52 than those who initiated TNFi (treatment difference [95% CI] for week 24:  $-0.831 [-1.086, -0.575]$  and for week 52:  $-0.910 [-1.204, -0.617]$ , both  $P < 0.001$ ) (Figure 1). Results of the primary effectiveness analysis were confirmed by sensitivity analyses (see Supplementary Table 4, available on the *Arthritis Care & Research* web site at <http://onlinelibrary.wiley.com/doi/10.1002/acr.23303/abstract>). Sensitivity analysis of change from baseline in any type of DAS28 (calculated using ESR, or C-reactive protein [CRP] if ESR was not available, and using DAS28 values entered by the investigator without each component), analysis of any type of DAS28 restricted to patients who had baseline disease activity assessments no longer than 2 weeks before their first biologic agent treatment, and a model making use of multiple imputation confirmed the primary effectiveness results; ANCOVA accounting additionally for seropositivity, age, disease duration, steroid use at baseline, history of malignant tumor, and treatment, as well as propensity score matching, also resulted in a significantly more change from baseline in DAS28-ESR to week 24 (see Supplementary Tables 1 and 4, available on the *Arthritis Care & Research* web site at <http://onlinelibrary.wiley.com/doi/10.1002/acr.23303/abstract>). The smallest between-groups treatment difference in all these supportive analyses was  $-0.748$ . The mean  $\pm$  SD treatment difference for the propensity score-based matched-pair analysis for DAS28-ESR was  $-1.05 \pm 2.07$ ;  $P < 0.001$ . Low patient numbers precluded viable effectiveness analysis of the data by monotherapy versus combination therapy with csDMARDs; only 28 patients treated with tocilizumab monotherapy and 42 treated with TNFi monotherapy were evaluable for the

primary effectiveness analysis. Analysis showed that among monotherapy patients, however, the treatment difference (95% CI) was not statistically significant for change from baseline in DAS28-ESR at week 24 or 52; monotherapy  $-0.287 [-1.194, 0.621]$ ;  $P = 0.530$  at week 24 and  $-0.598 [-1.289, 0.093]$ ;  $P = 0.089$  at week 52, and combination therapy  $-0.950 [-1.220, -0.680]$ ;  $P < 0.001$  at week 24 and  $-0.972 [-1.297, 0.647]$ ;  $P < 0.001$  at week 52 (see Supplementary Table 5, available on the *Arthritis Care & Research* web site at <http://onlinelibrary.wiley.com/doi/10.1002/acr.23303/abstract>).

Statistically significantly greater decreases from baseline to week 24 for patients who initiated tocilizumab compared with those who initiated TNFi were observed for ESR, CRP, and SJC (treatment differences [95% CI]:  $-13.23 [-15.51, -10.95]$ ,  $-6.67 [10.27, 3.07]$ , and  $-0.58 [-1.08, -0.08]$ ; all  $P < 0.05$ ) (Table 2). There was no statistically significant difference in TJC between the treatment groups at week 24 in the primary models. At week 52, the treatment difference was significant for ESR ( $-12.65 [-15.42, -9.88]$ ;  $P < 0.001$ ), SJC ( $-0.75 [-1.24, -0.27]$ ;  $P = 0.002$ ), and TJC ( $-1.22 [-2.04, -0.39]$ ;  $P = 0.004$ ), but not for CRP.

Decreases in CDAI and Simplified Disease Activity Index (SDAI) from baseline to weeks 24 and 52 were also significantly greater in patients who initiated tocilizumab treatment than in those who initiated TNFi treatment (treatment differences [95% CI]: CDAI:  $-3.48 [-5.48, -1.47]$  at week 24 and  $-4.60 [-6.71, 2.49]$  at week 52; SDAI:  $-3.23 [-5.81, -0.65]$  at week 24 and  $-3.25 [-6.12, -0.37]$  at week 52; all  $P < 0.05$ ). Significantly higher proportions of tocilizumab-



**Figure 3.** Drug survival on tocilizumab (TCZ) and tumor necrosis factor inhibitor (TNFi) (safety population—all patients; unadjusted analysis) based on Kaplan-Meier curve of time to discontinuation of biologic agent therapy. Patients for whom a biologic agent was not discontinued were censored at the study day of termination. *P* values were based on log rank test.

treated than TNFi-treated patients were in remission at week 24 according to DAS28-ESR (44.7% versus 29.7%;  $P < 0.001$ ) and CDAI (22.4% versus 14.6%;  $P = 0.015$ ), but not SDAI (21.3% versus 15.7%;  $P = 0.152$ ). By week 52, significantly higher proportions of tocilizumab-treated than TNFi-treated patients had achieved remission according to all 3 measures (Figure 2). Propensity score (calculated using logistic regression analysis with treatment group as the dependent variable and baseline factors as covariates) matched-pair analysis produced results comparable to those of the primary ANCOVA analysis of mean change from baseline to week 24 in CDAI (mean  $\pm$  SD treatment difference  $-3.22 \pm 20.29$ ;  $P = 0.0480$ ) (see Supplementary Table 6, available on the *Arthritis Care & Research* web site at <http://onlinelibrary.wiley.com/doi/10.1002/acr.23303/abstract>). There was a significant difference in improvement in patient-reported outcomes between patients who received tocilizumab and those who received TNFi as their first biologic agent, as demonstrated by a significantly greater decrease in HAQ DI and Functional Assessment of Chronic Illness Therapy fatigue scores at week 24 (Table 2).

**Drug survival.** Termination of initial biologic therapy was reported for 14.9% of patients who started tocilizumab and 27.4% of those who started TNFi; of these patients, 38.1% and 40.1%, respectively, terminated because of AEs and 23.8% and 48.8%, respectively, terminated because of lack of efficacy. It should be noted that patients could terminate their biologic-agent therapy but remain in the study or could withdraw from the study without terminating their biologic therapy. Drug survival analysis, in which observations for patients who completed the study on the initial biologic therapy and those who withdrew prematurely from the study without a biologic-agent discontinuation (e.g., patients lost to followup) were censored, showed that drug survival was significantly higher with tocilizumab than with TNFi ( $P < 0.001$ ) (Figure 3). The probability of tocilizumab

discontinuation was 9% (95% CI 6%, 12%) by week 24 and 15% (95% CI 12%, 19%) by week 52. The cumulative probability of TNFi discontinuation was 15% (95% CI 13%, 18%) at week 24 and 27% (95% CI 24%, 30%) by week 52.

**Safety.** AEs and SAEs were reported in similar proportions and at similar rates per 100 patient-years in patients who started tocilizumab and patients who started TNFi (Table 3). Infections and infestations were the most common AEs and SAEs in both groups; serious infections were reported in 8 (1.9% [8 events; 1.98 per 100 patient-years]) tocilizumab-treated patients and 26 (3.3% [39 events; 5.03 per 100 patient-years]) TNFi-treated patients (lower respiratory tract infection in 6 TNFi-treated patients and no tocilizumab-treated patients, pneumonia in 6 TNFi-treated patients and 2 tocilizumab-treated patients). Three patients in the tocilizumab group died (2 of pneumonia, 1 of cardiac failure), and 6 patients in the TNFi group died (1 of fecal peritonitis and multiorgan failure; 1 of surgical graft infection and 1 of sepsis; 1 of metastatic neoplasm and cerebrovascular accident; 1 of sepsis; 1 of metastatic neoplasm; and 1 of pneumonia and pericardial effusion). Two deaths from pneumonia (1 in each group) were deemed related to treatment, according to the investigator. Further details of the deaths can be found in Supplementary Table 7, available on the *Arthritis Care & Research* web site at <http://onlinelibrary.wiley.com/doi/10.1002/acr.23303/abstract>. Numeric differences were observed in the incidence of patients experiencing shifts in neutrophil counts, liver transaminase levels, or lipid profile parameters from normal at baseline to abnormal at week 24 or 52 between the treatment groups, but no difference was seen between weeks 24 and 52 for the individual treatment groups (Supplementary Table 8, available on the *Arthritis Care & Research* web site at <http://onlinelibrary.wiley.com/doi/10.1002/acr.23303/abstract>).

Table 3. Safety (safety population)\*

	TCZ (n = 423)	TNFi (n = 793)	Total (n = 1,216)
Exposure, no. patient-years	403.7	775.8	1179.5
AEs, no. (%)	208 (49.2)	449 (56.6)	657 (54.0)
Events, no.	501	1,011	1,512
Events, no. per 100 patient-years	124.10	130.32	128.19
AEs leading to withdrawal, no. (%)	9 (2.1)	13 (1.6)	22 (1.8)
Events, no.	9	19	28
Events, no. per 100 patient-years	2.23	2.45	2.37
AEs of special interest, no. (%)	34 (8.0)	42 (5.3)	76 (6.3)
Infections, no. (%)	88 (20.8)	205 (25.9)	293 (24.1)
SAEs, no. (%)	22 (5.2)	64 (8.1)	86 (7.1)
Events, no.	26	93	119
Events, no. per 100 patient-years	6.44	11.99	10.09
Serious infections, no. (%)	8 (1.9)	26 (3.3)	34 (2.8)
Events, no.	8	39	47
Events, no. per 100 patient-years	1.98	5.03	3.98
Deaths, no. (%)	3 (0.7)	6 (0.8)	9 (0.7)
Events, no. per 100 patient-years	0.74	0.77	0.76
AEs of special interest SOC and preferred term, no. (%)†			
Gastrointestinal disorders	0	3 (0.4)	3 (0.2)
Upper gastrointestinal hemorrhage	0	2 (0.3)	2 (0.2)
General disorders and administration site conditions	1 (0.2)	4 (0.5)	5 (0.4)
Injection site reaction	0	2 (0.3)	2 (0.2)
Immune system disorders	3 (0.7)	4 (0.5)	7 (0.6)
Hypersensitivity	2 (0.5)	3 (0.5)	5 (0.4)
Infections and infestations	9 (2.1)	20 (2.5)	29 (2.4)
Gastroenteritis	0	2 (0.3)	2 (0.2)
Lower respiratory tract infection	0	3 (0.4)	3 (0.2)
Pneumonia	2 (0.5)	6 (0.8)	8 (0.7)
Urinary tract infection	0	2 (0.3)	2 (0.2)
Injury, poisoning, and procedural complications	2 (0.5)	1 (0.1)	3 (0.2)
Infusion-related reaction	2 (0.5)	0	2 (0.2)
Investigations	6 (1.4)	2 (0.3)	8 (0.7)
ALT increased	2 (0.5)	0	2 (0.2)
Transaminases increased	4 (0.9)	1 (0.1)	5 (0.4)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	2 (0.5)	3 (0.4)	5 (0.4)
Metastatic neoplasm	0	2 (0.3)	2 (0.2)
Nervous system disorders	2 (0.5)	4 (0.5)	6 (0.5)
Cerebrovascular accident	0	2 (0.3)	2 (0.2)
Skin and subcutaneous tissue disorders	9 (2.1)	3 (0.4)	12 (1.0)
Dermatitis allergic	0	2 (0.3)	2 (0.2)
Rash	6 (1.4)	0	6 (0.5)

\* TCZ = tocilizumab; TNFi = tumor necrosis factor inhibitor; AEs = adverse events; SAEs = serious AEs; SOC = system organ class; ALT = alanine aminotransferase.  
† AEs reported in >1 patient in either treatment group.

## DISCUSSION

This is the first large-scale, multinational, prospective study to present real-life data on the use and drug survival of first-line intravenous tocilizumab and TNFi initiated in RA patients with an inadequate response to csDMARDs. Reflecting the observational nature of the study, there were no predefined interventions; the decision to initiate tocilizumab or TNFi was not based on protocol but on a decision made between the physician and the patient.

Significantly greater improvement in the DAS28-ESR was seen at weeks 24 (primary end point) and 52 for patients

who initiated tocilizumab as their first-line biologic agent compared with those who initiated TNFi. Since neither physicians nor patients were blinded to ESR or CRP results, there is a potential bias for overestimation of the effectiveness of tocilizumab influenced by changes in these markers of inflammation. Significantly greater improvement in CDAI was also observed for the tocilizumab group compared with the TNFi group. Calculation of the CDAI does not include the acute-phase reactants CRP or ESR, suggesting that DAS28 results were not solely influenced by the effect of inhibition of IL-6 signaling with tocilizumab on acute-phase reactants. Significantly higher proportions of tocilizumab-



treated patients than TNFi-treated patients achieved remission according to CDAI criteria ( $CDAI \leq 2.8$ ) at weeks 24 and 52, but it should be noted that for SDAI remission ( $SDAI \leq 3.3$ ), which does include calculation of CRP, the difference between tocilizumab and TNFi was significant only at week 52. Data on physical function, pain, and fatigue, though sometimes available in a minority of patients, were also consistent with the observation of greater effectiveness of tocilizumab. Tocilizumab was initiated as monotherapy more often than TNFi; however, the small number of patients in the primary effectiveness population prevented meaningful analysis of its effectiveness as monotherapy compared with combination therapy. The effectiveness of tocilizumab monotherapy compared with TNFi monotherapy should be investigated in a larger patient cohort.

Comparison between results of the current study and the published literature should account for differences in patient populations, study designs, and patterns and durations of treatment. Nevertheless, effectiveness results observed with tocilizumab in reports from clinical practice support the results of our study. For example, in ACT-SURE, an open-label study of csDMARD-inadequate responders treated with tocilizumab in clinical practice (15), 6-month CDAI and SDAI remission rates were 21.1% and 24.2%, respectively. In the current study, they were 22.4% and 21.3%, respectively. DAS28 remission rates in ACT-SURE (61.6%) were higher than in the current study (44.7%). Effectiveness data for TNFi agents are available from national registry databases. In the Consortium of Rheumatology Researchers of North America (CORRONA) registry, RA patients who started treatment with TNFi had a DAS28-ESR remission rate of 29.3% and a CDAI remission rate of 16.2% after 12 months (16). In the US Veterans Affairs Rheumatoid Arthritis (VARA) registry, the mean change from baseline in DAS28 after initiation of TNFi ranged from  $-0.77$  to  $-1.20$  (17), which is consistent with the mean change in the current study. The CORRONA and VARA registries collect data from patients in the US, whereas the current study did not include US patients. ADACTA is the only head-to-head trial to date comparing tocilizumab with a TNFi (adalimumab); it demonstrated the superior improvement in DAS28-ESR over 6 months with tocilizumab. Network meta-analyses of randomized controlled trial data have also been performed to investigate relative efficacies of biologic therapies in patients with RA. Comparable ACR response rates have been found between tocilizumab and TNFi agents in combination with DMARDs (18–20). DAS28 remission rates may be higher for tocilizumab than for abatacept, but this could be a result of the direct effect of tocilizumab on CRP levels (18). These network meta-analysis results are in contrast to the results of the current study, which showed better effectiveness for tocilizumab than TNFi (primarily in combination with DMARDs) as measured by DAS28-ESR and CDAI. Given the conflicting results between the literature and the current study and the limitations of comparing studies with different trial designs in network meta-analyses, prospective randomized trials are needed before robust conclusions can be drawn.

Patients who initiated tocilizumab in the current study had higher drug survival rates than those who initiated TNFi, which may be related to differences observed in

clinical effectiveness. The proportion of patients who remained on tocilizumab during this study (85.1%) is consistent with previously reported 6-month tocilizumab survival rates in clinical practice in the ACT-UP study (82.7%) (21). Similarly, the proportion of patients who remained on TNFi (72.6%) was consistent with the proportion reported in the CORRONA registry after 12 months of TNFi therapy (72%) (16). Comparison in an Australian health care database of biologic agents for the treatment of RA suggested that patients may be more persistent with tocilizumab and abatacept initiated as the first biologic-agent therapy than with subcutaneous TNFi agents. Combination therapy with methotrexate improved persistence with abatacept and subcutaneous TNFi but not with tocilizumab (22).

The safety profiles of tocilizumab and TNFi were comparable to the safety profiles reported in clinical trials and clinical practice (15,21,23–28). A recent Japanese prospective cohort study (29) comparing the safety of tocilizumab and TNFi in clinical practice reported that the risks for SAEs and serious infections were not significantly different during the first year of treatment when adjusted for baseline covariates.

Results of this study should be interpreted with an understanding of the limitation of potential biases associated with observational studies, including channeling bias. Confounding was addressed in a set of analyses adjusting for potential response predictors, including propensity score-based matching. All these analyses supported the key findings of the study. Results of the propensity score-based matched-pair analyses were comparable to those of the primary analysis for both DAS28-ESR and CDAI. Among other limitations were the amount of missing data for the effectiveness analysis (likely because of the observational nature of the study), the fact that DAS28-ESR was not used systematically in all centers (some centers used CRP for the calculation of DAS28), and the fact that delayed initiation of a prescribed treatment might have contributed to the lack of data for some baseline variables. Nevertheless, supportive efficacy analyses using end points with fewer missing values, including DAS28-CRP and using imputation of missing data, provided comparable results.

In conclusion, patients in the ACT-iON observational study who initiated tocilizumab as their first biologic-agent therapy after failure of csDMARDs experienced better drug survival and better improvements in DAS28-ESR, SJC, CDAI, and physical function than those who initiated TNFi. Additional prospective randomized controlled trials may be required to confirm these findings.

#### AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Choy had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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**Analysis and interpretation of data.** Choy, Bernasconi, Aassi, Molina, Epis.

### ROLE OF THE STUDY SPONSOR

Roche was involved in the study design, collection, analysis, and interpretation of data, writing the manuscript, and the decision to submit the manuscript for publication. Sara Duggan, PhD, and Meryl Mandle of ApotheCom provided medical writing services with funding from F. Hoffmann-La Roche Ltd. Publication of this article was not contingent upon approval by Roche.

### ADDITIONAL DISCLOSURES

Authors Bernasconi and Aassi are employees of F. Hoffmann-La Roche, Basel, Switzerland.

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