Arthritis Care & Research
DOI 10.1002/acr.23303

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

Ernest H. Choy, MD, FRCP,[1] Corrado Bernasconi, MD, PhD,[2] Maher Aassi, MD,[2] Jose Fernando Molina, MD,[3] Oscar Massimiliano Epis, MD[4]

[1]Cardiff University, Cardiff, United Kingdom; [2]F. Hoffmann-La Roche, Basel, Switzerland; [3]Centro Integral de Reumatología Reumalab, Medellín, Colombia; [4]S.C. Reumatologia, A.O. Ospedale Niguarda Ca' Granda, Milan, Italy

Corresponding Author

Prof. Ernest H. Choy

CREATE Centre

Section of Rheumatology, Division of Infection and Immunity

Cardiff University

Heath Park

Cardiff, Wales CF14 4XN, UK

Phone: +44 029 20687092, ext 87092

Email: choyeh@cardiff.ac.uk

Running head: Comparative effectiveness of tocilizumab and tumor necrosis factor inhibitors in rheumatoid arthritis

Received: Dec 07, 2016; Revised: Apr 27, 2017; Accepted: Jun 13, 2017

Word count: 3530 (limit, 3800)

Tables/figures: 3/3 (limit, 6) + 8/1 Supplementary

References: 29 (limit, 50)

Keywords: Disease-Modifying Antirheumatic Drugs (DMARDs), Biologics, Rheumatoid arthritis, Anti-TNF Drugs; interleukin-6, interleukin-6 receptor-alpha inhibitor, tocilizumab

Funding

This study was funded by Roche. Funding for manuscript preparation was provided by F. Hoffmann-La Roche Ltd.

Competing interests

Ernest H. Choy reports grants from Roche during the conduct of the study (>$10,000).

Corrado Bernasconi is a contractor for F. Hoffmann-La Roche (>$10,000).

Maher Aassi is an employee of F. Hoffmann-La Roche (>$10,000).

Jose Fernando Molina has nothing to disclose.

Oscar Massimiliano Epis has nothing to disclose.

ABSTRACT<< *253 words; maximum 250*>>

Objective. Compare clinical effectiveness between tocilizumab and tumor necrosis factor inhibitors (TNFi) in patients with rheumatoid arthritis 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 change from baseline in Disease Activity Score based on 28 joints–erythrocyte sedimentation rate (DAS28-ESR) at week 24 using analysis of covariance for between-group comparison. Secondary end points included Clinical Disease Activity Index (CDAI) and patient-reported outcomes at weeks 24 and 52.

Results. Of 1216 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 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/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 improved effectiveness and drug survival than those initiating TNFi in an observational setting.

Significance & Innovations

- To date, comparative efficacy of the interleukin-6 receptor-alpha monoclonal antibody tocilizumab and tumor necrosis factor inhibitors (TNFi) for the treatment of rheumatoid arthritis has been investigated in a single head-to-head trial of tocilizumab 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 tocilizumab compared with those who initiated TNFi in routine clinical practice as measured by Disease Activity Score based on 28 joints–erythrocyte sedimentation rate (DAS28-ESR) and clinical disease activity index (CDAI).

INTRODUCTION

Current American College of Rheumatology (ACR) and European League against Rheumatism (EULAR) 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 biologics are available for the treatment of RA; tumor necrosis factor inhibitors (TNFi), abatacept, and the interleukin-6 receptor-α inhibitor tocilizumab are recommended; under certain circumstances, rituximab may be used (2). However, evidence is lacking regarding which biologics should be used and in what sequence.

Only a few head-to-head clinical trials comparing biologics in patients with RA have been conducted to date. The randomized controlled phase 4 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 Disease Activity Score using 28 joints and the erythrocyte sedimentation rate (DAS28-ESR) from baseline to week 24. More tocilizumab-treated than adalimumab-treated patients achieved remission according to DAS28-ESR (DAS28 <2.6) and Clinical Disease Activity Index (CDAI ≤2.8) (3). The phase 3b AMPLE trial demonstrated similar clinical efficacy and inhibition of radiographic progression between abatacept and adalimumab in combination with methotrexate in patients with RA who had inadequate response to methotrexate (4). Rituximab was noninferior to TNFi treatment for change in DAS28-ESR in the open-label ORBIT trial in patients with RA who had 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 treatment after 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.

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 first biologic 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 United States or Canada, where the starting dose is 4 mg/kg (11,12)) as their first biologic. 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. The primary observation was mean change from baseline in DAS28-ESR at week 24. Secondary outcome measures included mean change from baseline in DAS28-ESR at week 52, swollen joint count (SJC), tender joint count (TJC), remission rates according to DAS28-ESR and CDAI, and patient-reported outcomes (PROs), including 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 2000 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 1225 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 ≥1 dose of a TNFi or tocilizumab). The primary effectiveness analysis population included all patients in the safety population administered their first biologic within 60 days after the previous RA disease activity measurement.

Missing values were not imputed for the primary analyses. Significance was determined as $P < 0.05$ 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 two treatment groups was based on an analysis of 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 (Supplementary Table S1). 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 to 14 days before their first biologic 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-group comparisons of the proportion of patients in DAS28 remission and other categorical variables. Drug survival was analyzed according to the Kaplan-Meier method, and between-group comparisons were performed based on the log-rank test.

RESULTS

Patient disposition. In total, 1216 patients initiated tocilizumab or TNFi therapy as their first biologic. 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 (Supplementary Figure S1; Supplementary Table S2). 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 (13.3%) patients withdrew from the study overall: 75 (17.7%) among patients who initiated tocilizumab as first biologic drug and 87 (11.0%) among patients who initiated TNFi. The most common reason was lost to follow-up, which occurred for 32 (7.6%) tocilizumab-treated patients and 36 (4.5%) TNFi-treated patients. Nine (2.1%) tocilizumab-treated and 13 (1.6%) TNFi-treated patients withdrew because of AEs, 4 (0.9%) tocilizumab-treated and 16 (2.0%) TNFi-treated patients withdrew because of lack of efficacy, and 8 (1.9%) tocilizumab-treated and 10 (1.3%) TNFi-treated patients withdrew consent. Overall, 34 (2.8%) patients 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% vs 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 (standard deviation [SD]) disease duration than patients who initiated TNFi (7.8 [7.3] vs 9.4 [9.0] years; $P = 0.014$). They also had slightly higher mean (SD) DAS28-ESR (5.8 [1.1] vs 5.5 [1.2]; $P = 0.030$) and SJC (9.0 [6.2] vs 7.4 [5.3]; $P < 0.001$) and more frequent oral corticosteroid use (60.5% vs 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%, tocilizumab-treated patients; 79.7%, TNFi-treated patients); in both groups, the median dose was 15 mg/week (Table 1). Additional baseline characteristics are shown in Supplementary Table S3.

Significant effects associated with the treatment choice (Supplementary Table S1) were country (United Kingdom and Spain were countries with clearly larger proportions of patients on TNFi), and intolerance was a reason for stopping the previous csDMARD (favoring the choice of tocilizumab: odds ratio [95% CI], 0.59 [0.42, 0.82]; $P = 0.002$) and current alcohol intake (favoring TNFi: odds ratio [95% CI], 1.83 [1.16, 2.88]; $P = 0.0092$).

Effectiveness. Patients who received tocilizumab as their first biologic had significantly higher change from baseline in DAS28-ESR to week 24 (primary end point) and week 52 than those who initiated TNFi (treatment difference [95% CI]: week 24, –0.831 [–1.086, –0.575]; 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 (Supplementary Table S4). 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 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 matching, also resulted in significantly higher change from baseline in DAS28-ESR to week 24 (Supplementary Tables S1 and S4). The smallest between-groups treatment difference in all these supportive analyses was –0.748. The mean (SD) treatment difference for the propensity score matched-pair analysis for DAS28-ESR was –1.05 (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 (Supplementary Table S5).

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 compared with those who initiated TNFi (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-treated than TNFi-treated patients were in remission at week 24 according to DAS28-ESR (44.7% vs 29.7%; $P < 0.001$) and CDAI (22.4% vs 14.6%; $P = 0.015$) but not SDAI (21.3% vs 15.7%; $P = 0.152$). By week 52, significantly higher proportions of tocilizumab-treated than TNFi-treated patients had achieved remission according to all three

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 (SD) treatment difference –3.22 (20.29; P = 0.0480) (Supplementary Table S6). There was a significant difference in improvement in PROs between patients who received tocilizumab as their first biologic and those who received TNFi, 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 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 discontinuation (eg, patients lost to follow-up) 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 (PY) 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; 1.98/100 PY]) tocilizumab-treated patients and 26 (3.3% [39 events; 5.03/100 PY]) 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 (fecal peritonitis and multiorgan failure; surgical graft infection and sepsis; metastatic neoplasm and cerebrovascular accident; sepsis; metastatic neoplasm; 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 S7.

Numerical 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 S8).

DISCUSSION

This is the first large-scale, multinational, prospective study to present real-life data on the use and survival of first-line intravenous tocilizumab and TNFi initiated in RA patients with 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 DAS28-ESR was seen at weeks 24 (primary end point) and 52 for patients who initiated tocilizumab as their first-line biologic 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 ≤2.8) at weeks 24 and 52, but it should be noted that for SDAI remission (SDAI ≤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 would have to 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 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), consistent with the mean change in the current study. The CORRONA and VARA registries collect data from patients in the United States, 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 compared with 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 biologics for the treatment of RA suggested that patients may be more persistent with tocilizumab and abatacept initiated as the first biologic therapy than with subcutaneous TNFi agents. Combination therapy with methotrexate improved persistence with abatacept and subcutaneous TNFis 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 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.

Role of the Study Sponsor

This study was funded by Roche. Funding for manuscript preparation was provided by F. Hoffmann-La Roche Ltd. The sponsor 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 on behalf of F. Hoffmann-La Roche Ltd.

Author Contributions

Conception and design, acquisition of data: EHC, CB, MA, JFM, OME

Analysis and interpretation of data: EHC, CB, MA, JFM

Drafting or revising article critically for important intellectual content: EHC, CB, MA, JFM

Approving the final version to be published: EHC, CB, MA, JFM, OME

Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated: EHC, CB, MA, JFM, OME

REFERENCES

1. Singh JA, Saag KG, Bridges SL Jr, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Rheumatol 2016;68:1-26.
2. Smolen JS, Landewe R, Breedveld FC, Buch M, Burmester G, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis 2014;73:492-509.
3. Gabay C, Emery P, van Vollenhoven R, Dikranian A, Alten R, Pavelka K, et al. Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. Lancet 2013;381:1541-50.
4. Schiff M, Weinblatt ME, Valente R, van der Heijde D, Citera G, Elegbe A, et al. Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: two-year efficacy and safety findings from AMPLE trial. Ann Rheum Dis 2014;73:86-94.
5. Porter D, van Melckebeke J, Dale J, Messow CM, McConnachie A, Walker A, et al. Tumour necrosis factor inhibition versus rituximab for patients with rheumatoid arthritis who require biological treatment (ORBIT): an open-label, randomised controlled, non-inferiority, trial. Lancet 2016;388:239-47.
6. Bergman GJ, Hochberg MC, Boers M, Wintfeld N, Kielhorn A, Jansen JP. Indirect comparison of tocilizumab and other biologic agents in patients with rheumatoid arthritis and inadequate response to disease-modifying antirheumatic drugs. Semin Arthritis Rheum 2010;39:425-41.

7. Yoshida K, Tokuda Y, Oshikawa H, Utsunomiya M, Kobayashi T, Kimura M, et al. An observational study of tocilizumab and TNF-alpha inhibitor use in a Japanese community hospital: different remission rates, similar drug survival and safety. Rheumatology (Oxford). 2011;50:2093-9.
8. Kaufmann J, Feist E, Roske AE, Schmidt WA. Monotherapy with tocilizumab or TNF-alpha inhibitors in patients with rheumatoid arthritis: efficacy, treatment satisfaction, and persistence in routine clinical practice. Clin Rheumatol 2013;32:1347-55.
9. Romao VC, Santos MJ, Polido-Pereira J, Duarte C, Nero P, Miguel C, et al. Comparative effectiveness of tocilizumab and TNF inhibitors in rheumatoid arthritis patients: data from the Rheumatic Diseases Portuguese Register, Reuma.pt. Biomed Res Int 2015;2015:279890.
10. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
11. ACTEMRA® (tocilizumab) injection, for intravenous use injection, for subcutaneous use [prescribing information]. South San Francisco, CA: Genentech, Inc.; November 2014.
12. ACTEMRA® (tocilizumab). Mississauga, ON, Canada: Hoffmann-La Roche Limited; 2015. http://www.rochecanada.com/content/dam/roche_canada/en_CA/documents/Research/ClinicalTrialsForms/Products/ConsumerInformation/MonographsandPublicAdvisories/Actemra/Actemra_PM_E.pdf. Accessed November 3, 2016.
13. Lobo FS, Wagner S, Gross CR, Schommer JC. Addressing the issue of channeling bias in observational studies with propensity scores analysis. Res Social Admin Pharm 2006;2:143-51.

14. Hudson M, Suissa S. Avoiding common pitfalls in the analysis of observational studies of new treatments for rheumatoid arthritis. Arthritis Care Res 2010;62:805-10.
15. Bykerk V, Ostor AJK, Alvaro-Gracia J, Pavelka K, Ivorra JA, Graninger W, et al. Tocilizumab in patients with active rheumatoid arthritis and inadequate responses to DMARDs and/or TNF inhibitors: a large, open-label study close to clinical practice. Ann Rheum Dis 2012:71:1950-4.
16. Greenberg JD, Reed G, Decktor D, Harrold L, Furst D, Gibofsky A, et al. A comparative effectiveness study of adalimumab, etanercept and infliximab in biologically naive and switched rheumatoid arthritis patients: results from the US CORRONA registry. Ann Rheum Dis 2012;71:1134-42.
17. Cannon GW, DuVall SL, Haroldsen CL, Caplan L, Curtis JR, Michaud K, et al. Persistence and dose escalation of tumor necrosis factor inhibitors in US veterans with rheumatoid arthritis. J Rheumatol 2014;41:1935-43.
18. Guyot P, Taylor P, Christensen R, Pericleous L, Poncet C, Lebmeier M, et al. Abatacept with methotrexate versus other biologic agents in treatment of patients with active rheumatoid arthritis despite methotrexate: a network meta-analysis. Arthritis Res Ther 2011;13:R204.
19. Orme ME, Macgilchrist KS, Mitchell S, Spurden D, Bird A. Systematic review and network meta-analysis of combination and monotherapy treatments in disease-modifying antirheumatic drug-experienced patients with rheumatoid arthritis: analysis of American College of Rheumatology criteria scores 20, 50, and 70. Biologics 2012;6:429-64.
20. Buckley F, Finckh A, Huizinga TW, Dejonckheere F, Jansen JP. Comparative efficacy of novel DMARDs as monotherapy and in combination with methotrexate in

rheumatoid arthritis patients with inadequate response to conventional DMARDs: a network meta-analysis. J Managed Care Specialty Pharm 2015;21:409-23.

21. Haraoui B, Casado G, Theander E, Czirják L, Taylor A, Mikes E, et al. Regional patterns of tocilizumab use, efficacy, and safety in patients with rheumatoid arthritis: interim results from a multinational observational study [abstract]. Ann Rheum Dis 2015;74:1042-3.
22. Jones G, Bird P, Hall S, Littlejohn G, Tymms K, Youssef P, et al. Dispensing of biologics prescribed for the treatment of rheumatoid arthritis in the Australian population [abstract]. Ann Rheum Dis 2015;74:246-7.
23. Genovese MC, Rubbert-Roth A, Smolen JS, Kremer J, Khraishi M, Gómez-Reino J, et al. Longterm safety and efficacy of tocilizumab in patients with rheumatoid arthritis: a cumulative analysis of up to 4.6 years of exposure. J Rheumatol 2013;40:768-80.
24. Schiff MH, Burmester GR, Kent JD, Pangan AL, Kupper H, Fitzpatrick SB, et al. Safety analyses of adalimumab (HUMIRA) in global clinical trials and US postmarketing surveillance of patients with rheumatoid arthritis. Ann Rheum Dis 2006;65:889-94.
25. Moreland LW, Cohen SB, Baumgartner SW, Tindall EA, Bulpitt K, Martin R, et al. Long-term safety and efficacy of etanercept in patients with rheumatoid arthritis. J Rheumatol 2001;28:1238-44.
26. Schiff M, Keiserman M, Codding C, Songcharoen S, Berman A, Nayiager S, et al. Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. Ann Rheum Dis 2008;67:1096-103.

27. Keystone E, Genovese MC, Klareskog L, Hsia EC, Hall S, Miranda PC, et al. Golimumab in patients with active rheumatoid arthritis despite methotrexate therapy: 52-week results of the GO-FORWARD study. Ann Rheum Dis 2010;69:1129-135.
28. Bykerk VP, Cush J, Winthrop K, Calabrese L, Lortholary O, de Longueville M, et al. Update on the safety profile of certolizumab pegol in rheumatoid arthritis: an integrated analysis from clinical trials. Ann Rheum Dis 2015;74:96-103.
29. Sakai R, Cho SK, Nanki T, Watanabe K, Yamazaki H, Tanaka M, et al. Head-to-head comparison of the safety of tocilizumab and tumor necrosis factor inhibitors in rheumatoid arthritis patients (RA) in clinical practice: results from the registry of Japanese RA patients on biologics for long-term safety (REAL) registry. Arthritis Res Ther 2015;17:74.

TABLES AND FIGURES

Table 1 Baseline demographics and treatments (safety population – all patients)

	TCZ n = 423	TNFi n = 793	*P*
Age, years, mean (SD)	54.3 (12.8)	55.2 (13.1)	0.171[n]
Disease duration, years, mean (SD)	7.8 (7.3)	9.4 (9.0)	0.014[n]
DAS28-ESR, mean (SD)[a]	5.8 (1.1)[e]	5.5 (1.2)[j]	0.030[n]
SJC, mean (SD)[a]	9.0 (6.2)[f]	7.4 (5.3)[k]	<0.001[n]
TJC, mean (SD)[a]	12.1 (6.9)[g]	12.1 (7.6)[k]	0.688[n]
CDAI, mean (SD)[a]	33.0 (13.5)[h]	31.2 (13.2)[l]	0.077[n]
HAQ-DI, mean (SD)[a]	1.5 (0.7)[e]	1.5 (0.7)[m]	0.968[n]
Initiated biologic as monotherapy, n (%)	119 (28.1)	127 (16.0)	<0.001[o]
Initiated biologic in combination with csDMARDs, n (%)	312 (73.8)	679 (85.6)	–
MTX, n (%)[b] [median dose, mg/week][c]	233 (74.7) [15.0]	541 (79.7) [15.0]	–
Hydroxychloroquine, n (%)[b]	70 (22.4)	179 (26.4)	–
Leflunomide, n (%)[b]	73 (23.4)	124 (18.3)	–
Sulfasalazine, n (%)[b]	37 (11.9)	122 (18.0)	–

Oral corticosteroid use, n (%)[d]	256 (60.5)	369 (46.5)	<0.001[o]
Oral corticosteroid dose, mg/day mean (SD)[d]	8.3 (5.55)[i]	7.3 (5.31)[l]	–
History of comorbid conditions, n (%)			
Other autoimmune disease	32 (7.6)	41 (5.2)	0.205[p]
Overlap syndrome	10 (2.4)	12 (1.5)	0.060[p]
Chronic hepatic impairment	11 (2.6)	27 (3.4)	0.774[p]
Severe and/or progressive infection	12 (2.8)	22 (2.8)	0.709[p]
Central nervous system demyelination	5 (1.2)	3 (0.4)	0.178[p]
Severe immunosuppression	0 (0.0)	2 (0.3)	0.518[p]
Malignant tumor	20 (4.7)	12 (1.5)	0.005[p]
Lymphoproliferative syndrome	1 (0.2)	0 (0.0)	0.016[p]
Angina/other heart disease	51 (12.1)	120 (15.1)	0.327[p]
Other clinically significant comorbidities	258 (61.0)	512 (64.6)	0.451[p]

[a]Primary effectiveness population.

[b]Percentages based on number of patients who initiated biologic in combination with csDMARDs.

[c]For MTX dose: TCZ, n = 233; TNFi, n = 538.

[d]Prednisone equivalent.

[e]n = 230. [f]n = 352. [g]n = 353. [h]n = 238. [i]n = 248. [j]n = 402. [k]n = 621. [l]n = 358. [m]n = 408.

[n]Based on Wilcoxon rank-sum test.

[o]Based on chi-square test for comparison of monotherapy and combination therapy between both treatment groups.

[p]Based on Fisher exact test.

CDAI, Clinical Disease Activity Index; DAS28, Disease Activity Score using 28 joints; csDMARD, conventional synthetic disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire–Disability Index; MTX, methotrexate; SD, standard deviation; SJC, swollen joint count; TCZ, tocilizumab; TJC, tender joint count; TNFi, tumor necrosis factor inhibitor.

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)**	**TCZ N = 390**	**TNFi N = 693**	**Difference (95% CI)**
ESR	–22.73 (–24.72, –20.75) n = 225	–9.50 (–11.11, –7.89) n = 456	–13.23 (–15.51, –10.95) p<0.001	–21.52 (–23.88, –19.16) n = 215	–8.87 (–10.87, –6.87) n = 411	–12.65 (–15.42, –9.88) *P* < 0.001
CRP	–11.01 (–14.13, –7.88) n = 177	–4.33 (–6.86, –1.81) n = 396	–6.67 (–10.27, –3.07) p < 0.001	–6.33 (–10.52, –2.14) n = 173	–5.22 (–8.71, –1.72) n = 348	–1.12 (–6.07, 3.84) *P* = 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) p = 0.024	–6.31 (–6.72, –5.90) n = 258	–5.56 (–5.91, –5.21) n = 503	–0.75 (–1.24, –0.27) *P* = 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) p = 0.123	–8.42 (–9.12, –7.72) n = 259	–7.21 (–7.80, –6.61) n = 501	–1.22 (–2.04, –0.39) *P* = 0.004
CDAI	–20.25 (–21.93, –	–16.78 (–18.28, –	–3.48 (–5.48, –	–22.85 (–24.63, –	–18.25 (–19.82, –	–4.60 (–6.71, –

	18.57)	15.27)	1.47)	21.06)	16.67)	2.49)
	n = 176	n = 286	p < 0.001	n = 162	n = 267	*P* < 0.001
SDAI	–21.39	–18.16	–3.23	–22.29	–19.05	–3.25
	(–23.67, –	(–20.05, –	(–5.81, –	(–24.79, –	(–21.13, –	(–6.12, –
	19.12)	16.28)	0.65)	19.80)	16.97)	0.37)
	n = 93	n = 193	p = 0.014	n = 91	n = 169	*P* = 0.027
HAQ-DI	–0.59	–0.45	–0.15	–0.59	–0.43	–0.16
	(–0.69, –	(–0.54, –	(–0.27, –	(–0.71, –	(–0.54, –	(–0.30, –
	0.49)	0.35)	0.02)	0.48)	0.32)	0.03)
	n = 169	n = 301	p = 0.020	n = 152	n = 255	*P* = 0.020
FACIT-	–7.15	–3.26	–3.89	–4.57	–1.78	–2.79
Fatigue	(–10.00, –	(–6.28, –	(–7.46, –	(–7.82, –	(–5.10,	(–6.76,
	4.30)	0.24)	0.33)	1.31)	1.54)	1.19)
	n = 64	n = 86	p = 0.032	n = 50	n = 77	*P* = 0.168
Pain VAS	–29.31	–23.65	–5.66	–32.96	–23.16	–9.80
	(–32.92, –	(–26.66, –	(–9.91, –	(–36.71 –	(–26.39, –	(–14.25, –
	25.69)	20.63)	1.41)	29.20)	19.92)	5.36)
	n = 204	n = 378	p = 0.009	n = 183	n = 336	*P* < 0.001

Data are adjusted means (95% CI). n values are the number of evaluable patients included in the ANCOVA model.

ANCOVA, analysis of covariance; CDAI, Clinical Disease Activity Index; CI, confidence interval; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FACIT, Functional Assessment of Chronic Illness Therapy; HAQ-DI, Health Assessment Questionnaire–Disability Index; MTX, methotrexate; SDAI, Simplified Disease Activity Index; SJC,

swollen joint count; TCZ, tocilizumab; TJC, tender joint count; TNFi, tumor necrosis factor inhibitor; VAS, Visual Analog Scale.

Table 3 Safety (safety population)

	TCZ n = 423	TNFi n = 793	Total N = 1216
Exposure, PY	403.7	775.8	1179.5
AEs, n (%)	208 (49.2)	449 (56.6)	657 (54.0)
[no. of events]	[501]	[1011]	[1512]
No. of events/100 PY	124.10	130.32	128.19
AEs leading to withdrawal, n (%)	9 (2.1)	13 (1.6)	22 (1.8)
[no. of events]	[9]	[19]	[28]
No. of events/100 PY	2.23	2.45	2.37
AEs of special interest, n (%)	34 (8.0)	42 (5.3)	76 (6.3)
Infections, n (%)	88 (20.8)	205 (25.9)	293 (24.1)
SAEs, n (%)	22 (5.2)	64 (8.1)	86 (7.1)
[no. of events]	[26]	[93]	[119]
No. of events/100 PY	6.44	11.99	10.09
Serious infections, n (%)	8 (1.9)	26 (3.3)	34 (2.8)
[no. of events]	[8]	[39]	[47]
No. of events/100 PY	1.98	5.03	3.98
Deaths, n (%)	3 (0.7)	6 (0.8)	9 (0.7)
No. of events/100 PY	0.74	0.77	0.76
AEs of special interest by SOC and preferred term, n (%)[a]			

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	2 (0.5)	3 (0.4)	5 (0.4)

unspecified (including cysts and polyps)			
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)

[a]AEs reported in >1 patient in either treatment group.

AE, adverse event; ALT, alanine aminotransferase; n, number of patients with event; PY, patient-years; SAE, serious adverse event; SOC, system organ class; TCZ, tocilizumab; TNFi, tumor necrosis factor inhibitor.

Figure Legends

Figure 1 Adjusted mean change from baseline to weeks 24 (primary end point) and 52 in DAS28-ESR (primary effectiveness population – all patients). Analyses were based on ANCOVA 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. ANCOVA, analysis of covariance; CI confidence interval; DAS28, Disease Activity Score using 28 joints; ESR, erythrocyte sedimentation rate; TCZ, tocilizumab; TNFi, tumor necrosis factor inhibitor.

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

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

Supplementary Figure S1 Patient disposition (A) and evaluable patients (B). DAS28, Disease Activity Score based on 28 joints; ESR, erythrocyte sedimentation rate; TCZ,

tocilizumab; TJC, tender joint count; TNFi, tumor necrosis factor inhibitor. [a]Excludes screen failures. Patients could have more than 1 reason for discontinuing the study.

Figure 1

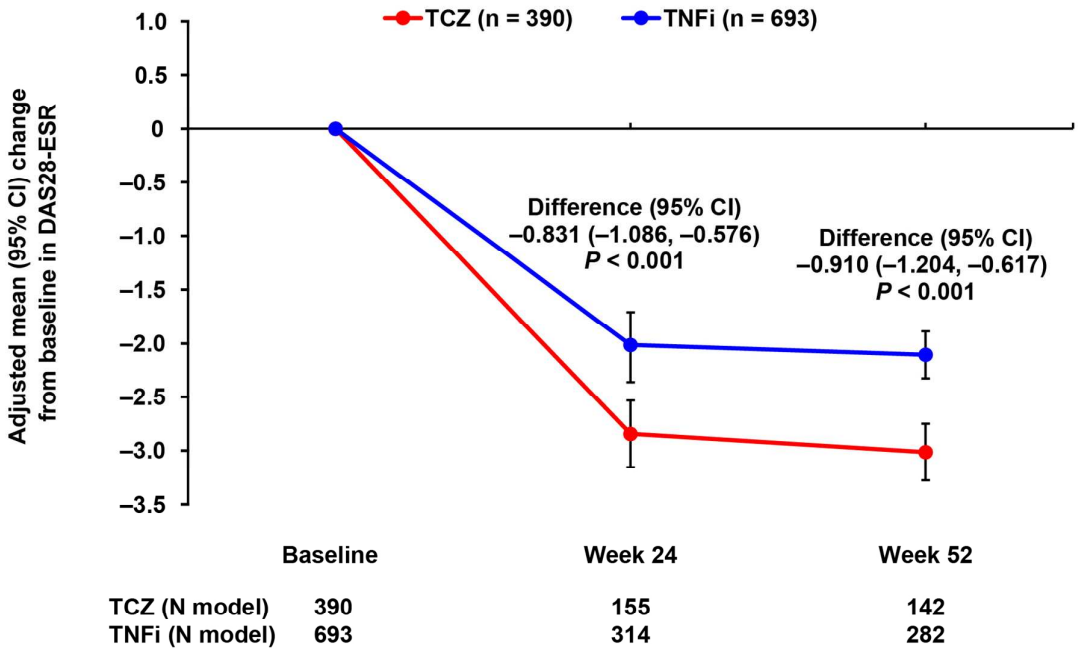

Figure 2

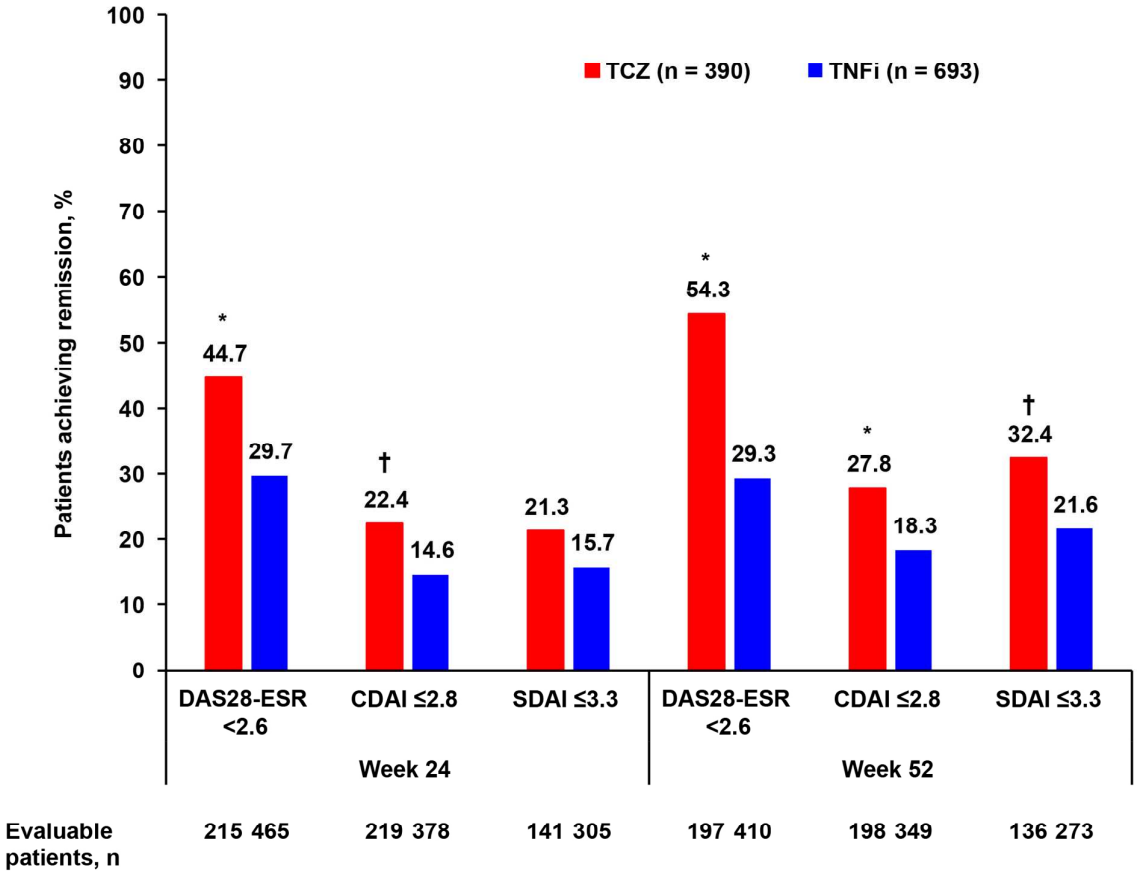

Figure 3