EXTENDED REPORT

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

Vivian P Bykerk,[1,2] Andrew J K Östör,[3] José Alvaro-Gracia,[4] Karel Pavelka,[5] José Andrés Román Ivorra,[6] Winfried Graninger,[7] William Bensen,[8] Michael T Nurmohamed,[9] Andreas Krause,[10] Corrado Bernasconi,[11] Andrea Stancati,[12] Jean Sibilia[13]

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[1]Inflammatory Arthritis Center, Hospital for Special Surgery, New York, USA
[2]Department of Rheumatology, Mount Sinai Hospital, Toronto, Ontario, Canada
[3]Department of Rheumatology, Addenbrookes Hospital, Cambridge, UK
[4]Rheumatology Service, Hospital Universitario de la Princesa, Madrid, Spain
[5]Institute of Rheumatology and Clinic of Rheumatology, Charles University, Prague, Czech Republic
[6]Rheumatology Service, Division of Rheumatology, Hospital Universitario La Fe, Valencia, Spain
[7]Division of Rheumatology, Medical University of Graz, Graz, Austria
[8]DeGroot School of Medicine, McMaster University, Hamilton, Canada
[9]Jan van Breemen Research Institute, VU University Medical Center, Amsterdam, Netherlands
[10]Department of Rheumatology, Medical Centre for Rheumatology Berlin Buch, Berlin, Germany
[11]Biostatistics, Roche, Basel, Switzerland
[12]Global Medical Affairs, Roche, Basel, Switzerland
[13]Department of Rheumatology, CHU Hautepierre, Strasbourg, France

Correspondence to
Vivian Bykerk, Inflammatory Arthritis Center, Hospital for Special Surgery, New York, New York, 10021, USA; USA; bykerkv@hss.edu

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ABSTRACT

Objective To evaluate the safety and efficacy of tocilizumab in clinical practice in patients with rheumatoid arthritis (RA) with inadequate responses (IR) to disease-modifying antirheumatic drugs (DMARDs) or both DMARDs and tumour necrosis factor α inhibitors (TNFis).

Methods Patients—categorised as TNFi-naive, TNFi-previous (washout) or TNFi-recent (no washout)—received open-label tocilizumab (8 mg/kg) every 4 weeks ± DMARDs for 24 weeks. Adverse events (AEs) and treatment discontinuations were monitored. Efficacy end points included American College of Rheumatology (ACR) responses, 28-joint disease activity score (DAS28) and European League Against Rheumatism responses.

Results Overall, 1681 (976 TNF-naive, 298 TNFi-previous and 407 TNFi-recent) patients were treated; 5.1% discontinued treatment because of AEs. The AE rate was numerically higher in TNFi-recent (652.6/100 patient-years (PY)) and TNFi-previous (653.6/100PY) than in TNFi-naive (551.1/100PY) patients. Serious AE rates were 18.0/100PY, 28.0/100PY and 18.6/100PY; serious infection rates were 6.0/100PY, 6.8/100PY and 4.2/100PY, respectively. At week 4, 36.5% of patients achieved ACR20 response and 14.9% DAS28 remission (<2.6); at week 24, 66.9%, 46.6%, 26.4% and 56.8% achieved ACR20/ACR50/ACR70 responses and DAS28 remission, respectively. Overall, 61.6% (TNFi-naive), 48.5% (TNFi-previous) and 50.4% (TNFi-recent) patients achieved DAS28 remission.

Conclusions In patients with RA who were DMARD-IR/TNFi-IR, tocilizumab ± DMARDs provided rapid and sustained efficacy without unexpected safety concerns.

INTRODUCTION

Up to 40% of patients with rheumatoid arthritis (RA) are inadequate responders (IR) to conventional disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor α inhibitor (TNFi) biological agents.[1 2] In these patients, tocilizumab—a humanised, monoclonal, anti-interleukin 6 receptor antibody—has marked clinical efficacy and a generally favourable safety/tolerability profile.[3–7]

This study (ACT-SURE) evaluated the safety/tolerability and efficacy of tocilizumab in a setting close to clinical practice in patients with moderate to severe RA who were receiving DMARDs before inclusion but were DMARD-IR and/or TNF-IR.

PATIENTS AND METHODS

Study design

This phase 3b, open-label, single-arm study included patients from 25 countries and 264 centres. Ethical and regulatory approval and patients' written informed consent were obtained in accordance with the Declaration of Helsinki, and good clinical practice was followed. Patients received 8 mg/kg tocilizumab intravenously every 4 weeks for 24 weeks. DMARDs were maintained at stable doses unless poorly tolerated, in which case tocilizumab was administered as monotherapy. TNFi therapy was discontinued, and patients could switch to tocilizumab with or without a washout period; one study goal was to evaluate the safety of a direct switch.

Study population

Patients were outpatients ≥18 years old with moderate to severe, active RA of ≥6-months' duration and were DMARD-IR, TNF-IR or both. Patients had a Disease Activity Score based on 28 joints (DAS28)>3.2 at screening and had to have received treatment with one or more DMARD, TNFi or both at a stable dose for ≥8 weeks before baseline. Patients receiving oral corticosteroids (≤10 mg/day prednisone or equivalent) or non-steroidal anti-inflammatory drugs had to receive stable doses for ≥25 of 28 days before baseline. See online Supplementary Methods for exclusion criteria.

Study assessments

The primary end point was incidence of adverse events (AEs) and serious AEs (SAEs). Secondary safety end points included rates of and reasons for treatment discontinuations.

Efficacy end points included American College of Rheumatology (ACR)20/50/70/90 responses, low disease activity (LDA; DAS28≤3.2) and DAS28

remission (DAS28<2.6) rates, DAS28 score and ACR core set parameters. Erythrocyte sedimentation rate was used to calculate DAS28. Clinical and Simplified Disease Activity Indices (CDAI and SDAI) and corresponding LDA (CDAI≤10, SDAI≤11) and remission (CDAI≤2.8, SDAI≤3.3) rates were evaluated post hoc.

Statistical analyses

Safety was assessed in patients who received one or more tocilizumab doses and had one or more postbaseline safety assessments. Efficacy was assessed in the intention-to-treat patients (those who received one or more doses of tocilizumab). Missing data were imputed using last-observation-carried-forward for joint counts only. Patients without data to compute the ACR response were classified as non-responders. For DAS28-based or similar categorical end points, only patients with a valid score were considered.

Descriptive statistics were used for all end points. CI based on the Poisson distributions were computed for AE incidences, and the Clopper–Pearson method was used for proportions. The standardised mortality ratio (SMR) was computed using data from the WHO Statistical Information System. For some analyses, patients were categorised by previous TNFi use: TNFi-naive (never received TNFi therapy), TNFi-previous (washout: TNFi therapy discontinued for >2 months before baseline) and TNFi-recent (TNFi therapy discontinued for ≤2 months before baseline).

RESULTS

Background characteristics

Of 1993 patients who were screened, 1683 were enrolled (84%), and two did not receive study medication (online supplementary figure S1). Safety and intention-to-treat populations included 1681 patients (976 TNFi-naive, 298 TNFi-previous, 407 TNFi-recent). RA duration was shortest among TNFi-naive patients. Baseline DAS28 scores were high and similar among the groups. Mean DMARD doses were close to maximal effective doses, and approximately 50% of patients were using corticosteroids, most frequently and at highest doses in the TNFi-previous group (table 1). In 239 patients, tocilizumab was used as monotherapy.

Safety

Overall, 215 patients (12.8%) discontinued tocilizumab prematurely; 86 patients (5.1%) did so because of AEs (19 (1.1%) because of infections). Four deaths were reported: streptococcal sepsis, cardiac arrest (two, both >3 weeks after the last tocilizumab dose) and aortic dissection (table 2). Two cases (streptococcal sepsis and cardiac arrest) were considered possibly related to tocilizumab. The SMR was 0.85.

Table 1 Baseline demographics and characteristics*

Characteristics	TNFi-naïve (n=976)	TNFi-previous use (n=298)	TNFi-recent use (n=407)	All patients (n=1681)
Female, % (n)	79 (773)	84 (250)	82 (333)	81 (1356)
Age, years	54 (12)	53 (12)	53 (12)	54 (12)
Duration of RA, years	8.2 (8.2)	11.2 (8.6)	11.7 (9.6)	9.6 (8.8)
DAS28	5.9 (1.2)	6.2 (1.2)	6.0 (1.3)	6.0 (1.2)
SJC	12.1 (8.7)	13.9 (9.6)	13.4 (9.9)	12.8 (9.2)
TJC	21.9 (14.4)	24.5 (15.8)	23.8 (15.6)	22.8 (15.0)
PtGA VAS	60.7 (21.0)	68.0 (21.4)	62.9 (20.8)	62.5 (21.2)
PhGA VAS	57.3 (17.3)	62.9 (17.5)	59.5 (18.9)	58.8 (17.9)
Pain VAS	55.3 (22.3)	63.1 (23.4)	58.7 (22.0)	57.5 (22.6)
CRP, mg/dl	1.7 (2.5)	2.4 (3.1)	2.2 (3.1)	1.9 (2.8)
ESR, mm/h	37.6 (25.5)	42.9 (28.9)	40.5 (28.1)	39.2 (26.8)
HAQ-DI	1.4 (0.6)	1.7 (0.6)	1.6 (0.6)	1.5 (0.6)
Previous DMARDs, n	0.5 (0.9)	2.5 (1.7)	2.5 (1.6)	1.3 (1.6)
Background DMARDs, % (n)				
0	7 (66)	21 (62)	27 (111)	14 (239)
1	68 (659)	71 (211)	62 (254)	67 (1124)
2	22 (211)	5 (16)	8 (31)	15 (258)
≥3	4 (40)	3 (9)	3 (11)	4 (60)
Patients receiving corticosteroids, % (n)	47.0 (459)	56.4 (168)	48.2 (196)	49.0 (823)
Mean corticosteroid dose,† mg/day	6.83	7.85	7.57	7.22
Leflunomide dose, mg/day	18.2 (5.1)	18.2 (4.5)	19.0 (3.0)	18.4 (4.6)
Methotrexate dose, mg/week	17.4 (5.3)	18.3 (12.9)	17.0 (5.8)	17.5 (7.3)
Sulfasalazine dose, g/day	1.9 (0.6)	1.7 (0.6)	2.0 (0.6)	1.9 (0.6)
Geographical distribution, % (n)				
Canada	11.2 (109)	10.4 (31)	5.9 (24)	9.8 (164)
Western Europe	61.3 (598)	81.5 (243)	87.5 (356)	71.2 (1197)
Other‡	27.6 (269)	8.1 (24)	6.6 (27)	19.0 (320)

*Data are presented as mean (SD), unless stated otherwise.
†Dose is expressed in prednisone equivalents for treated patients.
‡Other includes Australia, Czech Republic, Greece, Hungary, India, Poland, Romania, Saudi Arabia and Turkey.
CRP, C-reactive protein; DAS28, disease activity score based on 28 joints; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; IR, inadequate response; PtGA, patient global assessment; PhGA, physician global assessment; RA, rheumatoid arthritis; SJC, swollen joint count; TJC, tender joint count; TNFi, tumour necrosis factor inhibitor; TNFi-naive, patients who had never received TNFi therapy; TNFi-previous use, patients who had discontinued TNFi therapy for >2 months before baseline (washout period); TNFi-recent use, patients who had discontinued TNFi therapy for ≤2 months before baseline (no washout period); VAS, visual analogue scale.

Table 2 Principal safety outcomes

	TNFi-naïve (n=976)	TNFi-previous use (n=298)	TNFi-recent use (n=407)	All patients (n=1681)
Total PY	452.1	132.4	183.3	767.7
AE, % (n) (95% CI)	74.4 (726) (71.5 to 77.1)	80.2 (239) (75.2 to 84.6)	82.6 (336) (78.5 to 86.1)	77.4 (1301) (75.3 to 79.4)
AE, rate/100PY (95% CI)	551.1 (529.6 to 573.1)	653.6 (610.8 to 698.6)	652.6 (616.1 to 690.6)	593.0 (575.9 to 610.4)
SAE, % (n) (95% CI)	7.1 (69) (5.5 to 8.9)	11.1 (33) (7.7 to 15.2)	7.1 (29) (4.8 to 10.1)	7.8 (131) (6.6 to 9.2)
SAE, rate/100PY (95% CI)	18.6 (14.8 to 23.0)	28.0 (19.7 to 38.5)	18.0 (12.4 to 25.3)	20.1 (17.0 to 23.5)
Deaths, % (n)	0.3 (3)	0	0.2 (1)	0.2 (4)
Serious infections, % (n) (95% CI)	1.8 (18) (1.1 to 2.9)	2.7 (8) (1.2 to 5.2)	2.5 (10) (1.2 to 4.5)	2.1 (36) (1.5 to 3.0)
Serious infections, rate/100PY (95% CI)	4.2 (2.5 to 6.6)	6.8 (3.1 to 12.9)	6.0 (3.0 to 10.7)	5.1 (3.6 to 6.9)
AEs leading to withdrawal, % (n) (95% CI)	4.5 (44) (3.3 to 6.0)	7.0 (21) (4.4 to 10.6)	5.2 (21) (3.2 to 7.8)	5.1 (86) (4.1 to 6.3)
AEs leading to dose modification, % (n) (95% CI)	10.5 (102) (8.6 to 12.5)	11.1 (33) (7.7 to 15.2)	11.3 (46) (8.4 to 14.8)	10.8 (181) (9.3 to 12.3)
Infusion reactions,* % (n) (95% CI)	6.8 (66) (5.3 to 8.5)	7.4 (22) (4.7 to 11.0)	6.1 (25) (4.0 to 8.9)	6.7 (113) (5.6 to 8.0)
ALT shift from normal at baseline to 1.5–3×ULN at any time,† % (n)	14.7 (143)	9.4 (28)	9.1 (37)	12.4 (208)
ALT shift from normal at baseline to >3×ULN at any time,† % (n)	2.4 (23)	3.0 (9)	0.7 (3)	2.1 (35)
AST shift from normal at baseline to 1.5–3×ULN at any time,† % (n)	5.9 (58)	4.0 (12)	2.9 (12)	4.9 (82)
AST shift from normal at baseline to >3×ULN at any time,† % (n)	0.6 (6)	0.7 (2)	0.5 (2)	0.6 (10)

*Defined as an AE that occurred during infusion.
†Highest postbaseline value.
AE, adverse event; ALT, alanine aminotransferase; DMARD, disease-modifying anti-rheumatic drug; IR, inadequate response; PY, patient-years; SAE, serious adverse event; TNFi, tumour necrosis factor inhibitor; TNFi-naive, patients who had never received TNFi therapy; TNFi-previous use, patients who had discontinued TNFi therapy for >2 months before baseline (washout period); TNFi-recent use, patients who had discontinued TNFi therapy for ≤2 months before baseline (no washout period); ULN, upper limit of normal.

In total, 4552 AEs were reported in 1301 patients (77.4%). AE rate was lowest in TNFi-naive patients (table 2); 50.9% of patients had one or more AE considered unrelated, and 58.4% had one or more AE considered remotely, possibly or probably related to treatment.

Most commonly reported AEs were nasopharyngitis (6.9%), increased cholesterol (6.2%), headache (5.6%), nausea (4.7%), upper respiratory tract infection (4.2%), diarrhoea (4.1%) and increased alanine aminotransferase level (3.5%). Infections were reported in 594 patients (35.3%) and infusion reactions (AE within 24 h of infusion) in 291 patients (17.3%; 6.7% during infusion).

In total, 148 SAEs were reported in 131 patients (7.8%); 56.1% were considered unrelated to tocilizumab; 6.1%, 26.4% and 11.5% were considered remotely, possibly or probably related to treatment, respectively. SAE rates were similar between TNFi-naive and TNFi-recent patients and were higher in TNFi-previous patients (table 2). Serious infections, the most common SAEs, occurred in 36 patients (2.1%), most often in TNFi-previous and least often in TNFi-naive patients (table 2).

Laboratory parameters

Plasma alanine aminotransferase levels more than three times higher than the upper limit of normal were found in 3.3% of patients (table 2). An absolute neutrophil count $<2\times10^9$/l occurred in 33.5% of patients; 10.2% of patients had a decrease between 2 and 1.5×10^9/l. One patient experienced an absolute neutrophil count $<0.5\times10^9$/l but had no infection.

Efficacy

ACR response rates increased with time, with rapid onset (figure 1A). At week 24, 66.9%, 46.6%, 26.4% and 8.7% of patients had ACR20/ACR50/ACR70/ACR90 responses, respectively. At all time points, more TNFi-naive than TNFi-exposed patients achieved any level of response.

Rates of LDA and DAS28<2.6 increased over time (figure 1B). Overall, more TNFi-naive patients than patients with earlier TNFi exposure achieved LDA or DAS28<2.6 (figure 1B). Median time to DAS28<2.6 was 112 days. Overall, and within each TNFi subgroup, significant improvements in DAS28 scores were seen from week 4 through 24 ($p<0.0001$; all time points). Rates of LDA or remission according to CDAI and SDAI criteria increased over time in all groups and were highest in TNFi-naive patients (figure 1C,D).

European League Against Rheumatism categorical responses were consistent with LDA results: at week 24, 86.1% of TNFi-naive patients, 79.9% of TNFi-previous patients and 79.6% of TNFi-recent patients had good or moderate responses. Similar improvements were observed for ACR core set parameters (supplementary table S1), including Health Assessment Questionnaire-Disability Index (overall mean change −0.57).

DISCUSSION

Previous studies demonstrated the efficacy and safety of tocilizumab in controlled settings of clinical trials. In ACT-SURE, restrictions on concomitant medication were minimal, and the patient population was more representative of the broader spectrum of patients with RA in rheumatology practices. Most patients received DMARD treatment approximating the maximum effective dose, making this the first tocilizumab study in such an intensively treated population. Hence, ACT-SURE provides new information about the efficacy and safety of tocilizumab in a patient population resembling that expected in clinical practice.

Safety observations were consistent with previous tocilizumab studies.[3–8] SAEs and serious infections were less common than in a recent Japanese postmarketing surveillance programme (rates: 27.3/100PY and 9.1/100PY, respectively).[9] Safety was similar after patients switched from a TNFi to tocilizumab with or without washout, suggesting that a washout period may not be required. Compared with patients with previous TNFi exposure, TNFi-naive patients had better safety outcomes, consistent with tocilizumab and other biological agents. In tocilizumab studies, rates of SAEs and serious infections were slightly higher in TNF-IR[6] than TNFi-naive patients[3–5]; this is the first large study comparing these groups. In the adalimumab ReAct trial,

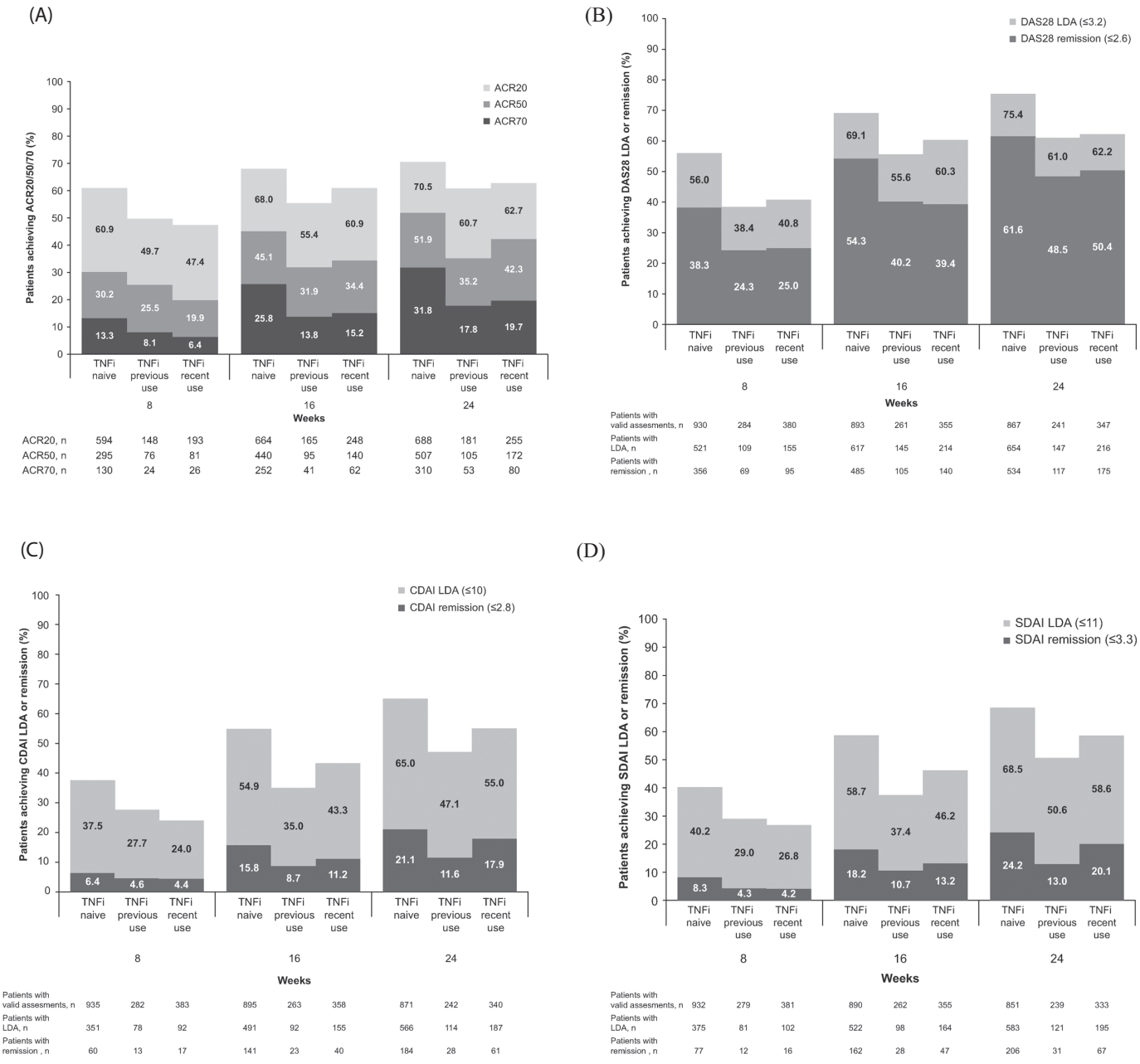

Figure 1 Patients achieving ACR20/ACR50/ACR70 responses (A) (all patients had valid assessments to week 24. Missing data were imputed for joint counts only, and non-responder imputation was used (ie, when constituent data were missing, these were not included in response computations, and patients were classified as non-responders)), DAS28 LDA/<2.6 (B), or LDA/remission according to CDAI (C) or SDAI (D) criteria (missing data were imputed for joint counts only) over time (ITT population). ACR, American College of Rheumatology; CDAI, Clinical Disease Activity Index; DAS28, Disease Activity Score based on 28 joints; DMARD, disease-modifying anti-rheumatic drug; ITT, intention to treat; LDA, low disease activity; SDAI, simplified disease activity index; TNFi, tumour necrosis factor inhibitor; TNFi naive, patients who had never received TNFi therapy; TNFi previous use, patients who had discontinued TNFi therapy for >2 months before baseline (washout period); TNFi recent use, patients who had discontinued TNFi therapy for ≤2 months before baseline (no washout period).

patient characteristics overlapped with those of ACT-SURE. Rates of SAEs (28.4/100PY vs 20.1/100PY) and serious infections (5.5/100PY vs 5.1/100PY) were also similar.[10] In ReAct, the latter was 10.0/100PY in TNFi-previous patients and 4.9/100PY in TNFi-naive patients.[11] However, exposure-normalised incidences reflect early treatment and, with TNFis, may decrease with longer exposure.[12] Mortality in ACT-SURE (rate: 0.24%, 0.52/100PY; SMR: 0.85) was slightly lower than reported for TNFi treatment in patients with RA (eg, 0.7/100PY for DMARD-IRs receiving etanercept[13]; SMR of 1.07 in ReAct[10]).

Overall, efficacy results from ACT-SURE are consistent with findings from pivotal international tocilizumab studies,[3–7] the recent US trial ROSE in DMARD-IR patients[8] and TAMARA, a German study similar in design to ACT-SURE but smaller (286 patients).[14] Marked improvements in disease status were noted already after 4 weeks, with continued improvements to week 24. In ACT-SURE, as in TAMARA and ReAct, patients without previous TNFi exposure experienced better efficacy than those previously treated with drugs from this class,[11] possibly because of less severe, less refractory disease at study entry. LDA

and remission rates were higher using DAS28 cut-off points than with CDAI/SDAI. This observation is in line with observations from other studies, whereas the gap appears to be larger with tocilizumab than with TNF inhibitors. This is probably attributable to the fact that tocilizumab strongly suppresses erythrocyte sedimentation rate, which has a large influence on DAS28.[15]

CONCLUSIONS

In this large-scale, international study mirroring patient profiles seen in rheumatology practice, the safety of tocilizumab was consistent with previous studies, regardless of the presence of a TNFi washout period. Results demonstrated a rapid onset of effect and continued improvements in efficacy over 6 months.

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Contributors VPB, AKJO, JA-G, KP, JARI, WB, JS were involved in the conception and design of the study, acquisition of data, or analysis and interpretation of data; drafting of manuscript and revising it critically for important intellectual content; final approval of the version to be published. WG was involved in the acquisition of data; revising the manuscript critically for important intellectual content; final approval of the version to be published. MTH was involved in the acquisition and interpretation of data; drafting of manuscript and revising it critically for important intellectual content; final approval of the version to be published. AK was involved in the conception and design of the study, acquisition of data, or analysis and interpretation of data; final approval of the version to be published. CB, AS were involved in the conception and design of the study, analysis and interpretation of data; drafting of manuscript and revising it critically for important intellectual content; final approval of the version to be published.

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Competing interests VPB has received consulting fees from Amgen, Pfizer, BMS, Roche, UCB; her institution has received grants from Amgen, Pfizer, BMS, UCB, Roche. AJKO has received consulting and expert testimony fees for expert opinion, honoraria for lectures, fees for the development of educational presentations and aids and travel expenses to attend conferences. JA-G has received consulting fees from Roche, BMS, UCB, Pfizer/Wyeth; lecture/speakers bureau fees from Roche, BMS, UCB, Pfizer/Wyeth, MSD/Schering-Plough, Abbott; travel expenses from Roche; and grants to his institution from Roche. KP has received board member fees from Roche, Pfizer, Amgen, UCB; consulting fees from Roche, MSD, Pfizer, UCB, BMS; and lecturer/speaker fees from Roche, MSD, Pfizer, UCB, BMS, Abbott. JARI has received travel expenses from Abbott, Roche; and grants from MSD, Roche. WG has received board member, consulting, and lecture/speaker fees from Roche, BMS, Pfizer, MSD, Abbott, UCB; and consulting fees/honorarium paid to his institution from Roche. WB has received board membership, consulting/honoraria, lecture/speaker fees; and has received grants paid to his institution. MTN has received consulting fees from Abbott, Roche, MSD, BMS, UCB, Wyeth, Sobi; speaker/lecture fees from Abbott, Roche, Pfizer; travel expenses from Roche, MSD; and grants from Roche, Abbott, Pfizer to his institution. AK has received board membership, consulting, lecture/speaker fees and travel expenses from Roche/Chugai. CB has received consulting fees from Roche Global Medical Affairs. AS was an employee of F Hoffmann-La Roche Ltd, Basel, Switzerland. JS has received board membership and consulting fees from Roche, MSD, Abbott, Pfizer, UCB.

Ethics approval Protocol approval by institutional review boards, ethics committees and/or regulatory authorities and patients' written informed consent were obtained in accordance with the Declaration of Helsinki, and good clinical practice was followed.

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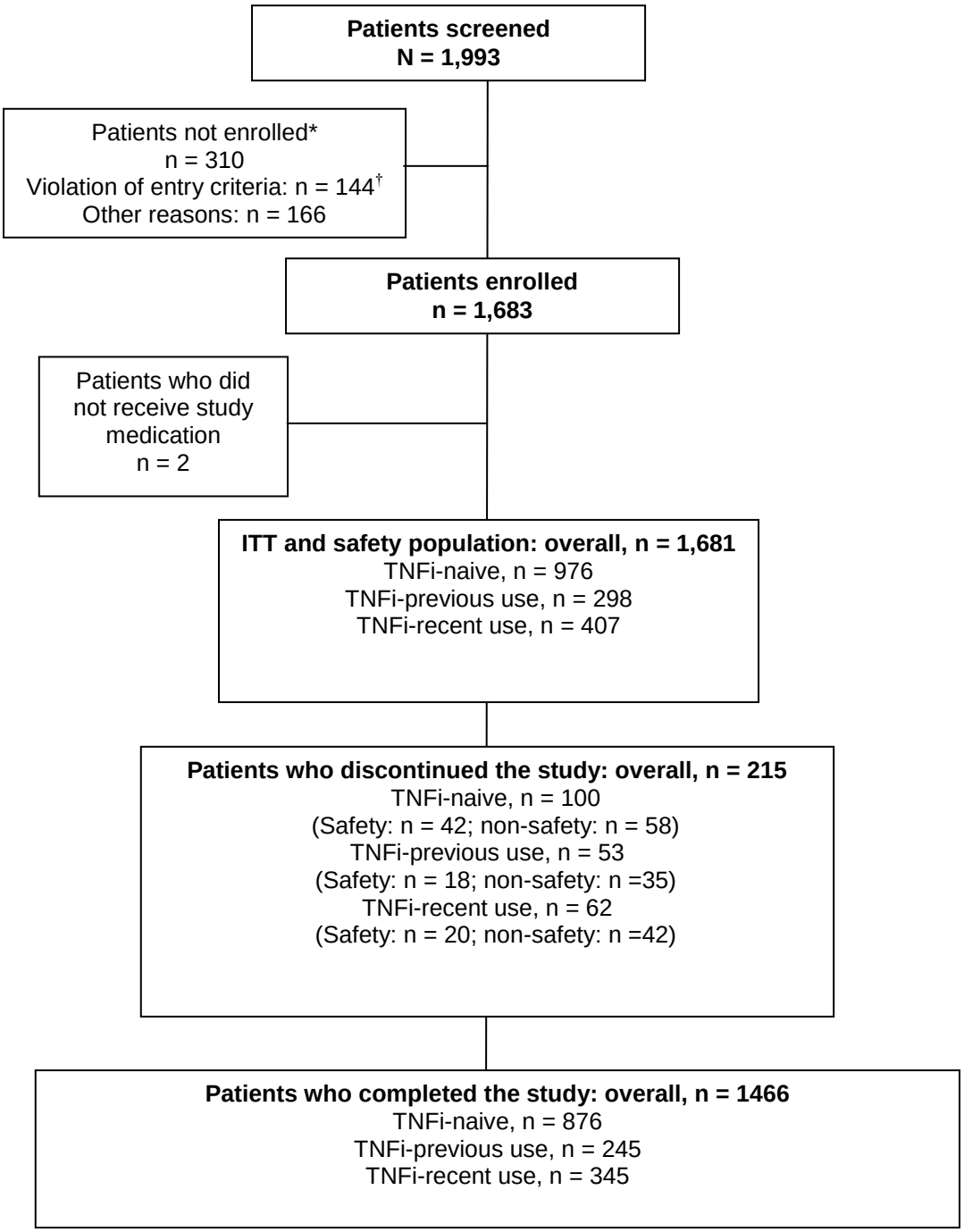
SUPPLEMENTARY MATERIAL

Supplementary Table S1 Mean (SD) improvements [% decrease] from baseline to week 24 in ACR core set parameters

	TNFi-naive (n = 976)	**TNFi-previous use (n = 298)**	**TNFi-recent use (n = 407)**
DAS28 change	3.52 (1.37) [59.9]	3.44 (1.44) [55.5]	3.17 (1.58) [53.2]
SJC, 66 joints	8.2 (10.5) [67.8]	8.5 (11.9) [61.2]	7.7 (12.1) [57.5]
TJC, 68 joints	14.6 (15.1) [66.7]	13.6 (15.8) [55.5]	13.2 (16.3) [55.5]
PGA VAS, mm	35.9 (25.3) [59.1]	37.9 (25.7) [55.7]	32.9 (26.0) [52.3]
PhGA VAS, mm	38.8 (21.5) [67.7]	40.7 (21.2) [64.7]	38.8 (23.7) [65.2]
Pain VAS, mm	32.3 (25.7) [58.4]	34.5 (26.9) [54.7]	29.9 (25.8) [50.9]
CRP, mg/dl	1.5 (2.3) [88.2]	2.3 (3.1) [95.8]	1.9 (2.9) [86.4]
ESR, mm/h	29.4 (23.0) [78.2]	36.9 (27.1) [86.0]	31.0 (26.8) [76.5]
HAQ-DI	0.59 (0.59) [42.8]	0.60 (0.61) [35.3]	0.50 (0.54) [31.3

ACR, American College of Rheumatology; CRP, C-reactive protein; DMARD, disease-modifying anti-rheumatic drug; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; PGA, patient global assessment; PhGA, physician global assessment; SJC, swollen joint count; TJC, tender joint count; TNFi, tumour necrosis factor inhibitor; TNFi-naive, patients who had never received TNFi therapy; TNFi-previous use, patients who had discontinued TNFi therapy for >2 months before baseline (washout period); TNFi-recent use, patients who had discontinued TNFi therapy for ≤2 months before baseline (no washout period); VAS, visual analogue scale.

Supplementary Figure S1 Summary of patient disposition. AE, adverse event; DMARD, disease-modifying anti-rheumatic drug; ITT, intent-to-treat; TCZ, tocilizumab; TNFi, tumour necrosis factor inhibitor; TNFi-naive, patients who had never received TNFi therapy; TNFi-previous use, patients who had discontinued TNFi therapy for >2 months before baseline (washout period); TNFi-recent use, patients who had discontinued TNFi therapy for ≤2 months before baseline (no washout period).



*Patients not enrolled: mean age 54.8 years, RA duration 9.3 years, tender joint count 20.2, swollen joint count 11.3

†Most common criteria leading to exclusion (each contributing to >5% of exclusions):

- CXR evidence of any clinically significant abnormality (9%)
- Patients should be screened for latent tuberculosis (TB), before biologics use, in accordance with local guidelines or Good Clinical Practice in each country. If screening results are positive, patients with latent TB should be treated with standard anti-mycobacterial therapy (at least 4 weeks) before initiation of TCZ and should have a negative CXR for active TB at screening. (8%)
- Active TB requiring treatment within the previous 3 years (7%)
- Known active current or history of recurrent bacterial, viral, fungal, mycobacterial or other infections (including but not limited to TB and atypical mycobacterial disease, clinically significant abnormalities on CXR as determined by the investigator, hepatitis B and C and herpes zoster, but excluding fungal infections of nail beds), or any major episode of infection requiring hospitalisation or treatment with IV antibiotics within 4 weeks of screening, or oral antibiotics within 2 weeks before screening (7%)

Supplementary Information

Methods

Inclusion Criteria

1. Male or non-pregnant, non-nursing female ≥18 years of age
2. Diagnosis of moderate to severe active RA (DAS28 ≥3.2) of ≥6-months' duration
3. Undergoing treatment on an outpatient basis
4. ≥1 non-biologic DMARDs at a stable dose for a period ≥8 weeks before treatment (day 1)
5. Inadequate clinical response to a stable dose of non-biologic DMARD or anti-TNF therapy
6. If receiving an oral corticosteroid, the dose must have been stable for at least 25 of 28 days before treatment (day 1)
7. Able and willing to give written informed consent and to comply with the requirements of the study protocol

Exclusion Criteria

1. Major surgery (including joint surgery) within 8 weeks before screening or planned major surgery within 6 months after enrollment
2. Diseases
    a. Rheumatic autoimmune disease other than rheumatoid arthritis (RA), including systemic lupus erythematosus, mixed connective tissue disease, scleroderma, polymyositis or significant systemic involvement secondary to RA (e.g. vasculitis, pulmonary fibrosis or Felty's syndrome)
    b. Interstitial pulmonary fibrosis but able to tolerate methotrexate (MTX) therapy; and Sjögren's syndrome with RA

c. Functional class IV as defined by the American College of Rheumatology (ACR) Classification of Functional Status in RA

d. Past history of or current inflammatory joint disease other than RA (e.g. gout, reactive arthritis, psoriatic arthritis, seronegative spondyloarthropathy, Lyme disease)

3. Treatment with

   a. Any investigational agent or with anakinra, calcineurin inhibitors (e.g. tacrolimus or cyclosporine), mycophenolate mofetil or mycophenolic acid sodium within 4 weeks (or 5 half-lives of investigational agent, whichever is longer) before screening; previous treatment with any cell-depleting therapies, including investigational agents (e.g. CAMPATH, anti-CD4, anti-CD5, anti-CD3, anti-CD19 and anti-CD20)

   b. Leflunomide in combination with MTX

   c. IV gamma globulin, plasmapheresis or Prosorba® column within 6 months before baseline

   d. Intra-articular or parenteral corticosteroids within 6 weeks before baseline

4. Immunisation with a live/attenuated vaccine within 4 weeks before baseline

5. Previous treatment with

   a. Abatacept

   b. Tocilizumab (an exception to this criterion may be granted for single-dose exposure on application to the sponsor on a case-by-case basis)

   c. Alkylating agents, such as cyclophosphamide and chlorambucil, or with total lymphoid irradiation

6. Laboratory values

a. Serum creatinine >142 μmol/L (1.6 mg/dl) in female patients and >168 μmol/L (1.9 mg/dl) in male patients and no active renal disease
b. Alanine aminotransferase (ALT [SGPT]) or aspartate aminotransferase (AST [SGOT]) >1.5 the upper limited of normal (ULN). (If initial sample showed ALT [SGPT] or AST [SGOT] >1.5 ULN, a second sample was to be taken and tested during the screening period)
c. Platelet count $<100 \times 10^9$/L (100,000/mm^3)
d. Haemoglobin <85 g/L (8.5 g/dl; 5.3 mmol/L)
e. White blood cell count $<1.0 \times 10^9$/L (1,000/mm^3), absolute neutrophil count $<1 \times 10^9$/L (1000/mm^3)
f. Absolute lymphocyte count $<0.5 \times 10^9$/L (500/mm^3)
g. Positive hepatitis B surface antigen or hepatitis C antibody
h. Total bilirubin >ULN (if initial sample showed bilirubin >ULN, a second sample was to be taken and tested during the screening period)
i. Triglycerides >10 mmol/L (>900 mg/dl) at screening (non-fasted)

7. Pregnant women or nursing (breastfeeding) mothers; or females of child-bearing potential who were not using reliable means of contraception, such as physical barrier (patient and partner), contraceptive pill or patch, spermicide and barrier or intrauterine device
8. History of severe allergic or anaphylactic reactions to human, humanised or murine monoclonal antibodies
9. Concomitant disorders
    a. Chest X-ray evidence of any clinically significant abnormality
    b. Evidence of serious uncontrolled concomitant cardiovascular, nervous system, pulmonary (including obstructive pulmonary disease), renal, hepatic,

endocrine (including uncontrolled diabetes mellitus) or gastrointestinal (GI) disease

c. Uncontrolled disease states, such as asthma, psoriasis and inflammatory bowel disease in which flares are commonly treated with oral or parenteral corticosteroids
d. Current liver disease as determined by the principal investigator. Patients with past history of ALT (SGPT) elevation were not to be excluded
e. Known active current or history of recurrent bacterial, viral, fungal, mycobacterial or other infections (including but not limited to tuberculosis and atypical mycobacterial disease, clinically significant abnormalities on chest x-ray as determined by the principal investigator, hepatitis B and C, and herpes zoster, but excluding fungal infections of nail beds), or any major episode of infection requiring hospitalisation or treatment with IV antibiotics within 4 weeks of screening, or oral antibiotics within 2 weeks before screening (does not apply to treatment of latent TB)
f. History of or currently active primary or secondary immunodeficiency
g. Evidence of active malignant disease, malignancies diagnosed within the previous 5 years (including hematological malignancies and solid tumours, except non-melanoma skin cancer that had been excised and cured), or breast cancer diagnosed within the previous 5 years
h. Active TB requiring treatment within the previous 3 years
    i. Patients were to be screened for latent TB, before biologics use, in accordance with local guidelines or Good Clinical Practice in their country. Patients with latent TB were to be treated with standard anti-

mycobacterial therapy (at least 4 weeks) before initiation of TCZ and to have negative CXR for active TB at screening.

i. Human immunodeficiency virus (HIV)–positive patient

10. History of alcohol, drug or chemical abuse within the 6 months before screening
11. Neuropathies or other painful conditions that might interfere with pain evaluation
12. Patients with lack of peripheral venous access
13. Body weight >150 kg

Sample Size

The following considerations justify the sample size of approximately 1,500 patients from the clinical point of view. We assume that at least 1,200 patients (i.e. 80% of the recruited patients) will conclude the study, providing a sample of patients with full exposure to the study drug from which the following can be expected:

- Assuming that a specific event (such an AE, treatment discontinuation, or transaminase elevation) occurs in 5% of patients in the study, the 95% CI around that incidence will extend from 3.8% to 6.2%. If the event occurs in 10% of patients, the CI will extend from 8.3% to 11.7%
- A TCZ-associated AE occurring in 1/1,000 patients would have a 70% chance to occur at least once in the patient population, and an event occurring in 1/522 patients would have a 90% chance to be detected

Results

Patient-Reported Outcomes

Health Assessment Questionnaire-Disability Index (HAQ-DI) clinical remission (HAQ-DI <0.5) was achieved by 31.5% of patients at week 24, at which time TNFi-recent patients had

a numerically smaller improvement (–0.50 ± 0.54; 31.3% decrease) than did TNFi-previous (–0.60 ± 0.61; 35.3% decrease) and TNFi-naive (–0.59 ± 0.59; 42.8% decrease) patients. The same was true at earlier visits (supplementary table 1). At week 4, 47.7% of patients experienced improvement in HAQ-DI ≥minimum clinically important difference (MCID; –0.22) from baseline, which increased to 72.7% at week 24.

SF-36 physical (PCS) and mental (MCS) component summary scores and all domain scores increased over time, with improvement ≥MCID for PCS (10 points) and each of the eight domains (5 points). At week 4, 19.1% and 25.9% of patients experienced improvement ≥MCID from baseline in PCS and MCS, respectively; at week 24, percentages increased to 44.9% and 39.6%, respectively. Bodily pain, vitality and mental health domain scores and MCS were restored to scores seen in the general population according to US normative data. FACIT-fatigue score improved by 10.76 (SD ±10.93) points from baseline to week 24; half the improvement was noted by week 4 (change from baseline, 5.01). At week 4, 49.0% of patients experienced improvement ≥MCID (4 points) from baseline, which increased to 69.5% at week 24.

Supplementary Information Table S1 Changes in laboratory parameters according to category of previous TNFi therapy

	TNFi-naive (n = 976)	**TNFi-previous use (n = 298)**	**TNFi-recent use (n = 407)**
ALT: % (n) patients with plasma level 1–3× ULN at any time post-BL after normal at BL	34.6 (338)	24.5 (73)	28.3 (115)
ALT: % (n) patients with plasma level >3× ULN at any time post-BL after normal at BL	2.4 (23)	3.0 (9)	0.7 (3)
AST: % (n) patients with plasma level 1–3× ULN at any time post-BL after normal at BL	24.6 (240)	16.4 (49)	15.2 (62)
AST: % (n) patients with plasma level >3× ULN at any time post-BL after normal at BL	0.6 (6)	0.7 (2)	0.5 (2)
Neutrophils: % (n) patients with absolute count $<1.0 \times 10^9$/L	2.9 (28)	2.3 (7)	4.2 (17)
Haemoglobin: mean (SD) change from baseline to week 24 (g/dl)	0.83 (1.10)	1.04 (1.23)	0.83 (1.26)
Total cholesterol: mean (SD) change from baseline to week 24 (mmol/L)	0.52 (0.93)	0.63 (0.90)	0.49 (0.93)
LDL cholesterol: mean (SD) change from baseline to week 24 (mmol/L)	0.28 (0.81)	0.37 (0.75)	0.26 (0.81)
HDL cholesterol: mean (SD) change from baseline to week 24 (mmol/L)	0.16 (0.28)	0.18 (0.32)	0.15 (0.28)
Triglycerides: mean (SD) change from baseline to week 24 (mmol/L)	0.17 (0.69)	0.22 (0.76)	0.18 (0.74)
Total cholesterol/HDL ratio: mean (SD) change from baseline to week 24	0.013 (0.792)	0.048 (0.760)	-0.009 (0.838)

ALT, alanine aminotransferase; BL, baseline; DMARD, disease-modifying anti-rheumatic drug; LDL, low-density lipoprotein; TNFi-naive, patients who had never received TNFi therapy; TNFi-previous use, patients who had discontinued TNFi therapy for >2 months before baseline (washout period); TNFi-recent use, patients who had discontinued TNFi therapy for ≤2 months before baseline (no washout period); TCZ, tocilizumab; ULN, upper limit of normal.