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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

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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 (TNFi).

Methods Patients—categorised as TNFi-naïve, TNFi-previous (washout) or TNFi-recent (no washout)—received open-label tocilizumab (8 mg/kg) every 4 weeks \pm 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 TNFi-naïve, 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-naïve (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-naïve), 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 \pm 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 TNFi-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, TNFi-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-naïve (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-naïve, 298 TNFi-previous, 407 TNFi-recent). RA duration was shortest among TNFi-naïve 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
Le unomide 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-naïve, 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 $1.5 \times \text{ULN}$ at any time, % (n)	14.7 (143)	9.4 (28)	9.1 (37)	12.4 (208)
ALT shift from normal at baseline to $>3 \times \text{ULN}$ at any time, % (n)	2.4 (23)	3.0 (9)	0.7 (3)	2.1 (35)
AST shift from normal at baseline to $1.5 \times \text{ULN}$ at any time, % (n)	5.9 (58)	4.0 (12)	2.9 (12)	4.9 (82)
AST shift from normal at baseline to $>3 \times \text{ULN}$ 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-naïve, 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-naïve 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-naïve 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-naïve 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 $<2 \times 10^9/\text{l}$ occurred in 33.5% of patients; 10.2% of patients had a decrease between 2 and $1.5 \times 10^9/\text{l}$. One patient experienced an absolute neutrophil count $<0.5 \times 10^9/\text{l}$ 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-naïve than TNFi-exposed patients achieved any level of response.

Rates of LDA and DAS28 <2.6 increased over time (figure 1B). Overall, more TNFi-naïve 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-naïve patients (figure 1C,D).

European League Against Rheumatism categorical responses were consistent with LDA results: at week 24, 86.1% of TNFi-naïve 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-naïve 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 TNFi-IR⁶ than TNFi-naïve patients³⁻⁵; this is the first large study comparing these groups. In the adalimumab ReAct trial,

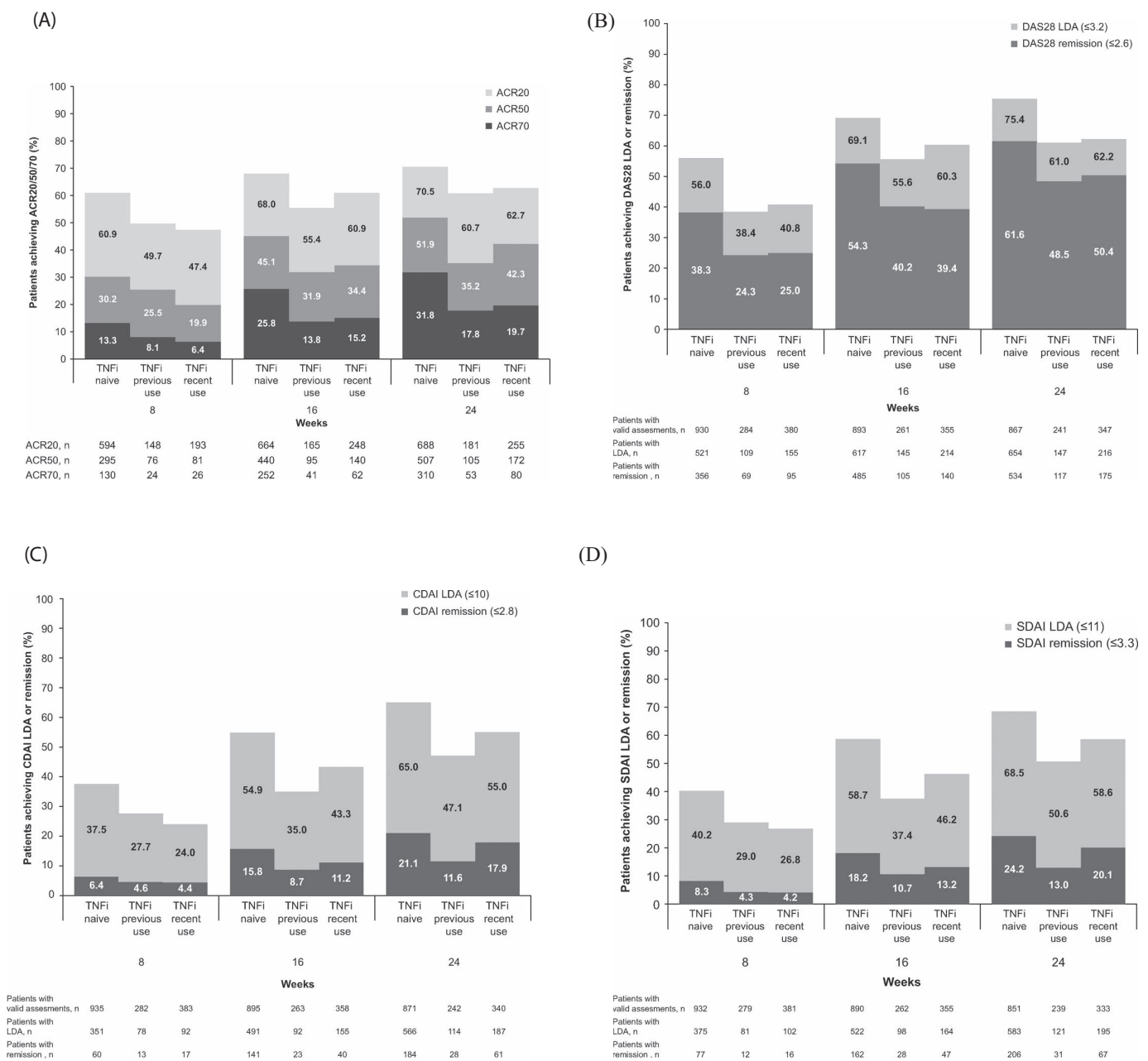


Figure 1 Patients achieving ACR20/ACR50/ACR70 responses (A) (all patients had valid assessments to week 24. Missing data were imputed for joint counts only, and non-responder imputation was used (ie, when constituent data were missing, these were not included in response computations, and patients were 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-naïve patients and 4.9/100PY in TNFi-naïve 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 etanercept¹³; SMR of 1.07 in ReAct¹⁰).

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 patients⁸ 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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Competing interests VPB has received consulting fees from Amgen, P zer, BMS, Roche, UCB; her institution has received grants from Amgen, P zer, 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, P zer/Wyeth; lecture/speakers bureau fees from Roche, BMS, UCB, P zer/Wyeth, MSD/Schering-Plough, Abbott; travel expenses from Roche; and grants to his institution from Roche. KP has received board member fees from Roche, P zer, Amgen, UCB; consulting fees from Roche, MSD, P zer, UCB, BMS; and lecturer/speaker fees from Roche, MSD, P zer, 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, P zer, 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, P zer; travel expenses from Roche, MSD; and grants from Roche, Abbott, P zer 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, P zer, UCB.

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REFERENCES

1. Bathon JM, Martin RW, Fleischmann RM, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *N Engl J Med* 2000;**343**:1586–93.
2. Maini RN, Breedveld FC, Kalden JR, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. *Arthritis Rheum* 1998;**41**:1552–63.
3. Smolen JS, Beaulieu A, Rubbert-Roth A, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. *Lancet* 2008;**371**:987–97.
4. Jones G, Sebba A, Gu J, et al. Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study. *Ann Rheum Dis* 2010;**69**:88–96.
5. Genovese MC, McKay JD, Nasonov EL, et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. *Arthritis Rheum* 2008;**58**:2968–80.
6. Emery P, Keystone E, Tony HP, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. *Ann Rheum Dis* 2008;**67**:1516–23.
7. Maini RN, Taylor PC, Szechinski J, et al. Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. *Arthritis Rheum* 2006;**54**:2817–29.
8. Yazici Y, Curtis JR, Ince A, et al. Efficacy of tocilizumab in patients with moderate to severe active rheumatoid arthritis and a previous inadequate response to disease-modifying antirheumatic drugs: the ROSE study. *Ann Rheum Dis* 2012;**71**:198–205.
9. Koike T, Harigai M, Inokuma S, et al. Postmarketing surveillance of tocilizumab for rheumatoid arthritis in Japan: interim analysis of 3881 patients. *Ann Rheum Dis* 2011;**70**:2148–51.
10. Burmester GR, Mariette X, Montecucco C, et al. Adalimumab alone and in combination with disease-modifying antirheumatic drugs for the treatment of rheumatoid arthritis in clinical practice: the Research in Active Rheumatoid Arthritis (ReAct) trial. *Ann Rheum Dis* 2007;**66**:732–9.
11. Bombardieri S, Ruiz AA, Fardellone P, et al. Effectiveness of adalimumab for rheumatoid arthritis in patients with a history of TNF-antagonist therapy in clinical practice. *Rheumatology (Oxford)* 2007;**46**:1191–9.
12. Galloway JB, Hyrich KL, Mercer LK, et al. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. *Rheumatology (Oxford)* 2011;**50**:124–31.
13. Moreland LW, Weinblatt ME, Keystone EC, et al. Etanercept treatment in adults with established rheumatoid arthritis: 7 years of clinical experience. *J Rheumatol* 2006;**33**:854–61.
14. Burmester GR, Feist E, Kellner H, et al. Effectiveness and safety of the interleukin 6-receptor antagonist tocilizumab after 4 and 24 weeks in patients with active rheumatoid arthritis: the first phase IIIb real-life study (TAMARA). *Ann Rheum Dis* 2011;**70**:755–9.
15. Smolen JS, Aletaha D. Interleukin-6 receptor inhibition with tocilizumab and attainment of disease remission in rheumatoid arthritis: the role of acute-phase reactants. *Arthritis Rheum* 2011;**63**:43–52.