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 (TNFis).

Methods Patients—categorised as TNF-naïve, TNF-previous (washout) or TNF-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 endpoints included American College of Rheumatology (ACR) responses, 28-joint disease activity score (DAS28) and European League Against Rheumatism responses.

Results Overall, 1681 (976 TNF-naïve, 298 TNF-previous and 407 TNF-Recent) patients were treated; 5.1% discontinued treatment because of AEs. The AE rate was numerically higher in TNF-Recent (652.6/100 patient-years) than in TNF-naïve (551.1/100PY) patients. Serious AE rates were 18.0/100PY, 28.0/100PY and 18.6/100PY, 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% (TNF-naïve), 48.5% (TNF-previous) and 50.4% (TNF-recent) patients achieved DAS28 remission.

Conclusions In patients with RA who were DMARD-IR/TNF-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 (ACR20/50/70/90) responses, low disease activity (LDA; DAS28≤3.2) and DAS28≤1.3.
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 (CDAIs:10, SDAIs:11) and remission (CDAIs:2.8, SDAIs: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: >2 months before baseline), 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-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*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>TNFi-naïve (n=976)</th>
<th>TNFi-previous use (n=298)</th>
<th>TNFi-recent use (n=407)</th>
<th>All patients (n=1681)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, % (n)</td>
<td>79 (773)</td>
<td>84 (250)</td>
<td>82 (333)</td>
<td>81 (1356)</td>
</tr>
<tr>
<td>Age, years</td>
<td>54 (12)</td>
<td>53 (12)</td>
<td>53 (12)</td>
<td>54 (12)</td>
</tr>
<tr>
<td>Duration of RA, years</td>
<td>8.2 (8.2)</td>
<td>11.2 (8.5)</td>
<td>11.7 (8.6)</td>
<td>9.6 (8.8)</td>
</tr>
<tr>
<td>DAS28</td>
<td>5.9 (12)</td>
<td>6.2 (1.2)</td>
<td>6.0 (1.3)</td>
<td>6.0 (1.2)</td>
</tr>
<tr>
<td>SJC</td>
<td>12.1 (8.7)</td>
<td>13.9 (9.6)</td>
<td>13.4 (9.9)</td>
<td>12.8 (9.2)</td>
</tr>
<tr>
<td>TJC</td>
<td>21.9 (14.4)</td>
<td>24.5 (15.8)</td>
<td>23.8 (15.6)</td>
<td>22.8 (15.0)</td>
</tr>
<tr>
<td>PGA VAS</td>
<td>60.7 (21.0)</td>
<td>68.0 (21.4)</td>
<td>62.9 (20.8)</td>
<td>62.5 (21.2)</td>
</tr>
<tr>
<td>PhGA VAS</td>
<td>57.3 (17.3)</td>
<td>62.9 (17.5)</td>
<td>59.5 (18.9)</td>
<td>58.8 (17.9)</td>
</tr>
<tr>
<td>Pain VAS</td>
<td>55.3 (22.3)</td>
<td>63.1 (23.4)</td>
<td>58.7 (22.0)</td>
<td>57.5 (22.6)</td>
</tr>
<tr>
<td>CRP , mg/dl</td>
<td>37.6 (25.5)</td>
<td>42.9 (28.9)</td>
<td>40.5 (28.1)</td>
<td>39.2 (26.8)</td>
</tr>
<tr>
<td>ESR, mm/h</td>
<td>1.4 (0.8)</td>
<td>1.7 (0.6)</td>
<td>1.6 (0.6)</td>
<td>1.5 (0.6)</td>
</tr>
<tr>
<td>HAQ-DI</td>
<td>0.5 (0.9)</td>
<td>2.5 (1.7)</td>
<td>2.5 (1.6)</td>
<td>1.3 (1.6)</td>
</tr>
<tr>
<td>Background DMARDs, % (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>7 (66)</td>
<td>21 (62)</td>
<td>27 (111)</td>
<td>14 (239)</td>
</tr>
<tr>
<td>1</td>
<td>68 (659)</td>
<td>71 (211)</td>
<td>62 (254)</td>
<td>67 (1124)</td>
</tr>
<tr>
<td>2</td>
<td>22 (211)</td>
<td>5 (16)</td>
<td>8 (31)</td>
<td>15 (258)</td>
</tr>
<tr>
<td>≥3</td>
<td>4 (40)</td>
<td>3 (9)</td>
<td>3 (11)</td>
<td>4 (60)</td>
</tr>
<tr>
<td>Patients receiving corticosteroids, % (n)</td>
<td>47.0 (459)</td>
<td>56.4 (168)</td>
<td>48.2 (196)</td>
<td>49.0 (823)</td>
</tr>
<tr>
<td>Mean corticosteroid dose, mg/day</td>
<td>6.83</td>
<td>7.85</td>
<td>7.57</td>
<td>7.22</td>
</tr>
<tr>
<td>Le unomide dose, mg/day</td>
<td>18.2 (5.1)</td>
<td>18.2 (4.5)</td>
<td>19.0 (3.0)</td>
<td>18.4 (4.6)</td>
</tr>
<tr>
<td>Methotrexate dose, mg/week</td>
<td>17.4 (5.3)</td>
<td>18.3 (12.9)</td>
<td>17.0 (5.8)</td>
<td>17.5 (7.3)</td>
</tr>
<tr>
<td>Sulphasalazine dose, g/day</td>
<td>1.9 (0.6)</td>
<td>1.7 (0.6)</td>
<td>2.0 (0.6)</td>
<td>1.9 (0.6)</td>
</tr>
<tr>
<td>Geographical distribution, % (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td>11.2 (109)</td>
<td>10.4 (31)</td>
<td>5.9 (24)</td>
<td>9.8 (164)</td>
</tr>
<tr>
<td>Western Europe</td>
<td>61.3 (598)</td>
<td>81.5 (243)</td>
<td>87.5 (356)</td>
<td>71.2 (1197)</td>
</tr>
<tr>
<td>Other</td>
<td>27.6 (269)</td>
<td>8.1 (24)</td>
<td>6.6 (27)</td>
<td>19.0 (320)</td>
</tr>
</tbody>
</table>

*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; PGA, physician global assessment; PhGA, patient 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 (washout period), VAS, visual analogue scale.


1951
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% 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%), diarhoea (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 86 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 $1.5\times10^9/l$. 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. Rates of SAEs and serious infections were less common than in a recent Japanese postmarketing surveillance programme (rates: 27.3/100PY and 9.1/100PY, respectively). 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 TNFi-IR than TNFi-naive patients; this is the first large study comparing these groups. In the adalimumab ReAct trial,
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. In ReAct, the latter was 10.0/100PY in TNFi-previous patients and 4.9/100PY in TNFi-naive patients. However, exposure-normalised incidences reflect early treatment and, with TNFis, may decrease with longer exposure. Mortality in ACT-SURE (rate: 0.24%, 0.52/100PY; SMR: 0.85) was slightly lower than reported for 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).

Overall, efficacy results from ACT-SURE are consistent with findings from pivotal international tocilizumab studies, the recent US trial ROSE in DMARD-IR patients and TAMARA, a German study similar in design to ACT-SURE but smaller (286 patients). 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, 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. MTH 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. WG 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, P zer, BMS, Roche, JCB; her institution has received grants from Amgen, P zer, BMS, UCB, Roche. AKJO 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/speaker bureau fees from Roche, BMS, UCB, P zer/Wyeth; MWD/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. WB has received board member consulting, and lecture/speaker fees; speaker fees and has received grants paid to his institution from Roche. CB has received board membership, consulting/ honoraria, lecture/speaker fees; and has received grants paid to his institution. MTH has received consulting fees from Abbott, Roche, MSD, BMS, UCB, Wyeth, Sobis; 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. JS 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
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