Clinical efficacy and safety maintained up to 5 years in patients with rheumatoid arthritis treated with tocilizumab in a randomised trial

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Abstract

Objective

To report 5-year efficacy and safety in rheumatoid arthritis (RA) patients with active disease treated with tocilizumab.

Methods

LITHE was a 2-year, randomised, placebo-controlled study of tocilizumab in RA patients (ClinicalTrials.gov, NCT00106535), with an additional 3-year, open-label extension. Patients were randomly assigned to tocilizumab (4 or 8 mg/kg IV) or placebo every 4 weeks + methotrexate. They could receive rescue with tocilizumab from week 16; after week 52, patients could switch to open-label tocilizumab 8 mg/kg. Radiographs were analysed by randomised treatment using the Genant-modified Total Sharp Score (GmTSS). Patients with at least baseline, week 104 and post-week 104 radiographs were included. Clinical and safety data were pooled for all patients who received ≥1 dose of tocilizumab; results are presented from the first tocilizumab dose.

Results

1,149 patients were included with 4,380 patient-years of exposure; 34% received 5 years of treatment. Mean 5-year change in GmTSS revealed greater inhibition of radiographic progression in tocilizumab patients than placebo patients (1.34 vs. 3.02), with the greatest annualised progression rate in year 1. Overall, 53% of tocilizumab and 35% of placebo patients experienced no progression (GmTSS ≤0). Clinical benefit was maintained – determined by ACR response, DAS28-ESR <2.6, EULAR good/moderate response and Boolean remission – as was physical function. The safety profile over 5 years was similar to that over 2 years.

Conclusion

Over 5 years, tocilizumab + MTX inhibited radiographic progression and maintained improvements in signs and symptoms and physical function in MTX-inadequate responders with active disease; no new safety signals occurred.

Key words

rheumatoid arthritis, biological therapy, radiography

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Introduction

Interleukin-6 (IL-6) is central in the pathogenesis of rheumatoid arthritis (RA) and is involved in the development of systemic symptoms, articular inflammation and bone resorption, with subsequent joint damage (1-4). IL-6 effects are mediated through signalling pathways involving soluble and membrane-bound IL-6 receptors (1). Elevated levels of IL-6 have been shown to correlate with disease activity in RA patients (4, 5).

Tocilizumab is a humanised monoclonal antibody that blocks IL-6 receptor-α, thus inhibiting IL-6–mediated proinflammatory signalling (6-8). The efficacy of tocilizumab in alleviating RA signs and symptoms, inhibiting structural joint damage and improving physical function has been demonstrated in phase 3 and open-label studies (7, 9-17). LITHE (ClinicalTrials.gov, NCT00106535) was a three-arm randomised, placebo-controlled, phase 3 multicentre study with up to 5 years of observation that evaluated tocilizumab in patients with active RA who were incomplete responders to methotrexate (MTX). During the first 2 years, patients receiving tocilizumab plus MTX demonstrated statistically significant inhibition of radiographic progression and improvements in disease signs and symptoms (14). Here we report the final 5-year data in LITHE.

Patients and methods

Study design

LITHE was a 1-year, double-blind, parallel-group study with open label in year 2 and a subsequent 3-year extension (Supplementary Fig. S1A). Patients were randomly assigned 1:1:1 to placebo or tocilizumab (4 or 8 mg/kg) every 4 weeks (q4w) intravenously with MTX 10–25 mg every week (orally or parenterally). Patients with inadequate response to treatment, defined as <20% improvement from baseline in swollen and tender joint count (SJC, TJC), were eligible for two-step rescue between weeks 16 and 48. In the first step, placebo patients were treated with tocilizumab 4 mg/kg q4w, and tocilizumab 4 mg/kg-treated patients were increased to 8 mg/kg q4w (patients receiving tocilizumab 8 mg/kg continued on that dose). In the second rescue step, if there was <20% improvement in SJC and TJC after three doses of the first rescue, patients received tocilizumab 8 mg/kg q4w. Patients who did not achieve ≥20% improvement in SJC and TJC after three doses of the second-step rescue discontinued treatment. All patients received open-label tocilizumab 8 mg/kg + MTX from week 52, except those with ≥70% improvement in SJC and TJC at two consecutive visits during year 1; these patients could opt to remain on blinded therapy or to receive open-label tocilizumab 8 mg/kg. After the completion of year 2, patients could enter an optional open-label extension (years 3–5), during which they received tocilizumab 8 mg/kg + MTX q4w. Radiographic progression was assessed at baseline and at weeks 52, 104, 152, 200 and 260.

Study population

Eligible patients were aged ≥18 years, had active RA of ≥6 months' duration and experienced inadequate response to ≥12 weeks of MTX (stable dose of 10-25 mg/week for 8 weeks before baseline). Patients had to have radiographic evidence of ≥1 joint with erosion, as determined by a central reading. All other conventional synthetic disease-modifying anti-rheumatic drugs and biologic DMARDs were withdrawn before randomisation with appropriate washout periods, but patients who discontinued anti-tumour necrosis factor therapy because of inadequate response or safety issues were excluded. Oral corticosteroids and non-steroidal anti-inflammatory drugs were allowed if the dose was stable for ≥6 weeks before baseline. Complete eligibility criteria have been published (13).

Analyses

All analyses were exploratory; only descriptive analyses are provided.

Radiographic analyses

Radiographic analyses were conducted in the radiographic population (all patients who received ≥1 dose of tocilizumab in year 3 and who had radiographs taken at baseline, at week 104

and after week 104). Radiographic endpoints included change from baseline in Genant-modified Total Sharp Score (GmTSS), erosion, joint space narrowing (JSN) score, annualised progression rate (APR) and proportions of patients with no radiographic progression (change from baseline in GmTSS ≤0). Radiographic data collected after withdrawal or during rescue were included; missing week 260 data were imputed with linear extrapolation using all available data for an individual patient to predict the missing value. There was no imputation of missing data for APR calculation. Patients were analysed by randomised treatment in the week 260 analyses. Logistic regression was used to analyse proportions of patients who experienced no radiographic progression.

Signs and symptoms

Analyses of American College of Rheumatology (ACR) 20/50/70/90 response, major clinical response (ACR70 maintained for ≥24 weeks), Health Assessment Questionnaire–Disability Index (HAQ-DI) score, Clinical Disease Activity Index (CDAI) remission (CDAI ≤2.8), ACR/European League Against Rheumatism (EULAR) Boolean remission (18) and Disease Activity Score at 28 joints using erythrocyte sedimentation rate (DAS28-ESR) <2.6 (remission) and ≤3.2 (low disease activity) were conducted in the tocilizumab population (all patients who received ≥1 dose of tocilizumab). The last-observation-carried-forward method was used for missing SJC and TJC data; no imputation was used for missing HAQ-DI score, C-reactive protein (CRP) level, ESR or Visual Analog Scale assessments (CRP was used for the calculation of ACR response; if missing, ESR was substituted). Any patient with a missing measurement at a specific time point was excluded from summary descriptive statistics at that time point.

Safety

Safety analyses were conducted in the tocilizumab population and included exposure to study medication, withdrawal, adverse events (AEs), AEs leading to withdrawal, death, laboratory assessments, concomitant medications, vital signs and immunogenicity. Protocol-defined criteria for tocilizumab discontinuation in patients with alanine aminotransferase/aspartate aminotransferase (ALT/AST) elevations have been reported (14). AEs were classified according to the Medical Dictionary for Regulatory Activities, version 15.0. AE rates were calculated per 100 patient-years (PY) of exposure (number of events/total exposure × 100). Immunogenicity was assessed throughout the study (Methods in Data Supplement).

Results

Patient population

In total, 1,196 patients were randomly assigned: 392 to placebo + MTX, 399 to tocilizumab 4 mg/kg + MTX and 399 to tocilizumab 8 mg/kg + MTX. Six patients received no study medication (one, placebo + MTX arm; two, tocilizumab 4 mg/kg + MTX; three, tocilizumab 8 mg/kg + MTX). The tocilizumab population eventually consisted of 1,149 patients. This population was predominantly female (83%) with the mean age 51.9 years (Supplementary Table S1). The radiographic population consisted of 803 patients; of these, 258 were originally assigned to placebo + MTX, and 545 were originally assigned to tocilizumab + MTX. Demographics of patients who entered the long-term extension were similar to those of the overall population.

Patient disposition

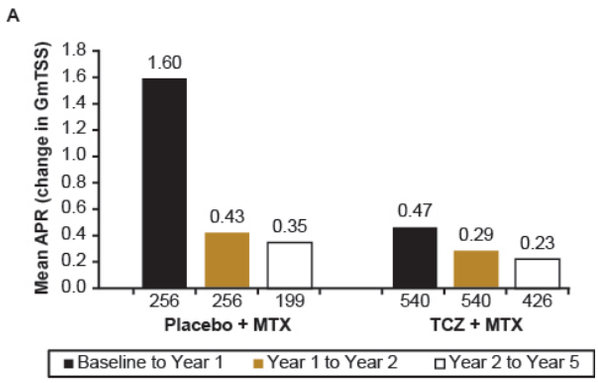
During the first year of treatment, 50% of placebo + MTX patients escaped to tocilizumab; most did so before week 24. After week 52, most (62%-68%) patients switched to open-label tocilizumab 8 mg/kg across all groups. At 104 weeks, 73% (287/392) of patients originally assigned to placebo + MTX and 78% (619/797) assigned to tocilizumab (4 mg/kg or 8 mg/kg) + MTX completed treatment. In total, 704 (58.9%) enrolled patients completed visits up to week 260.

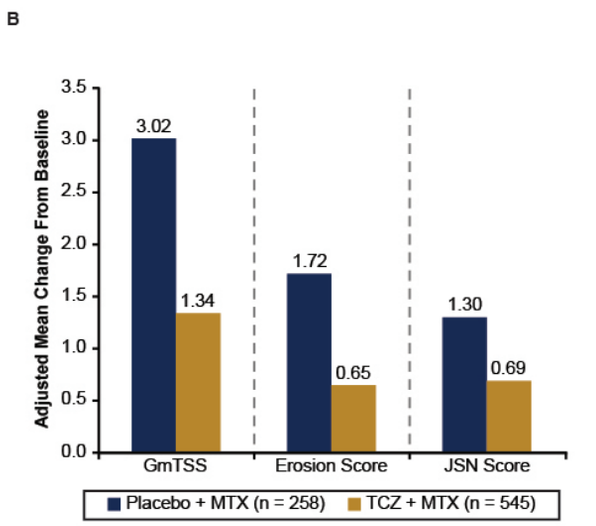
In the tocilizumab population, 387 patients (33.7%) received ≥5 years (264 weeks) of tocilizumab treatment, whereas 445 (38.7%) withdrew after receiving ≥1 dose of tocilizumab. Withdrawals were attributed to safety in 239 patients (20.8%, including 22 deaths [1.9%]) and non-safety reasons in 206 patients (17.9%; included insufficient therapeutic response [3.0%], refused treatment [9.6%], failure to return [2.3%] and other [3.1%]). Numbers of patients who withdrew over time are shown in Supplementary Fig. S1B. Mean duration of exposure to tocilizumab was 3.81 years for the tocilizumab population, with half the patients receiving tocilizumab for ≥4.69 years. During each 24-week period between years 3 and 5 (weeks 96–264), the withdrawal rate was similar at each time point (range, 1.8%–3.3%) and was lower than the withdrawal rate during the first 72 weeks after tocilizumab initiation (range, 5.1%–7.1%).

Radiographic analysis

In the radiographic population, the mean APR for GmTSS observed from baseline to year 1 was 0.47 in the tocilizumab + MTX group and 1.60 in the placebo + MTX group (Fig. 1A). Mean APR in the placebo + MTX group substantially decreased after patients switched to tocilizumab at the end of year 1 (mean APR 0.43 from year 1 to year 2) and remained low between years 2 and 5 (mean APR 0.35). Differences in APR for the tocilizumab + MTX group between years 1 and 2 and between years 2 and 5 (mean APR 0.29 and 0.23, respectively) were not as pronounced as those seen in the placebo + MTX group because they were already low in year 1.

At week 260 (end of year 5), the adjusted mean change in GmTSS from baseline was 1.34 for the tocilizumab + MTX group and 3.02 for the placebo + MTX group, suggesting greater inhibition in radiographic changes in patients randomly assigned to tocilizumab + MTX than to placebo + MTX who switched to tocilizumab (Fig. 1B). Similarly, the adjusted mean change in erosion and JSN scores from baseline at week 260 were 0.65 and 1.72, respectively, for the tocilizumab + MTX group and 0.69 and 1.30, respectively, for the placebo + MTX group in patients randomly assigned to tocilizumab





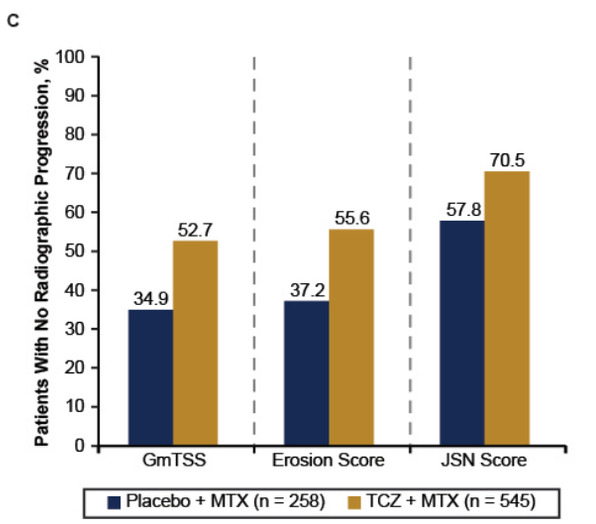


Fig. 1.
Radiographic analysis.
A. Mean APR in GmTSS. APR calculations could not be performed for seven patients who did not have week 52 x-ray assessments.
B. Radiographic progression from baseline at week 260 by original treatment.
C. Proportions of patients with no radiographic progression from baseline at week 260 (radiographic population). APR: annualised progression rate; GmTSS: Genant-modified Total Sharp Score; JSN: joint space narrowing; MTX: methotrexate; TCZ: tocilizumab.

rather than to placebo who switched to tocilizumab (Fig. 1B).

No progression of radiographic damage at week 260 was reported in 34.9% of patients assigned to placebo + MTX, compared with 52.7% of those assigned to tocilizumab + MTX; similar results were observed for erosion and JSN scores (Fig. 1C).

Signs and symptoms analysis

In the tocilizumab population, the proportions of patients treated with tocilizumab + MTX who achieved ACR20/50/70/90 responses increased rapidly over the first 24 weeks; ACR20/50/70/90 rates at week 24 were 59.9%/30.8%/12.5%/1.7%, respectively. Using observed data, maintenance of efficacy was observed through week 260 in patients who remained in the study (82.9%/64.9%/42.1%/16.7%, respectively; Fig. 2A). The proportions of patients who maintained ACR20/50/70 responses over time are shown in Supplementary Fig. S2A-C. At the end of 5 years, 21% of patients had experienced major clinical response (ACR70 maintained for ≥24 weeks), and 15% had maintained ACR70 response for ≥48 weeks (Suppl. Fig. S2C). This analysis requires patients to demonstrate ACR70 response at each consecutive visit.

Mean DAS28-ESR declined steadily through the first 2 years and was then maintained through week 260 (Supplementary Fig. S3A). The proportions of patients with DAS28-ESR ≤3.2 and DAS28-ESR <2.6 were maintained to week 260; 73.8% of patients who remained in the LTE had DAS28-ESR ≤3.2, and 59.4% had DAS28-ESR <2.6 (Fig. 2B). Proportions of patients who maintained DAS28-ESR <2.6 for ≥24 weeks were relatively stable over time. At week 260, 27.9% had DAS28-ESR <2.6 for ≥24 weeks, and 20.8% experienced it for ≥48 weeks (Supplementary Fig. S3B). As with the ACR analysis, patients had to have consecutive DAS28-ESR <2.6 responses to be included. At week 260, 71.7% had maintained EULAR good/moderate response for ≥24 weeks, and 35.0% had maintained EULAR good/moderate response for ≥192 weeks (Supplementary Fig. S4).

The proportion of patients achieving Boolean remission increased through the first 2 years and remained stable through week 260 (Fig. 2C). At week 260, 21.5% (103/480) of remaining patients fulfilled Boolean remission criteria, and 31.7% (152/480) fulfilled CDAI remission criteria (CDAI ≤2.8).

Improved HAQ-DI scores were maintained through week 260 (Fig. 2D). At week 260, 313 of 444 (70.5%) patients showed improved HAQ-DI scores with reductions of ≥0.25 points, including 62.2%, 55.4% and 37.6% of patients who showed reductions of 0.3, 0.5 and 0.75 points, respectively.

Safety

Year 2 (14) and year 5 AE profiles were comparable, with no increases in

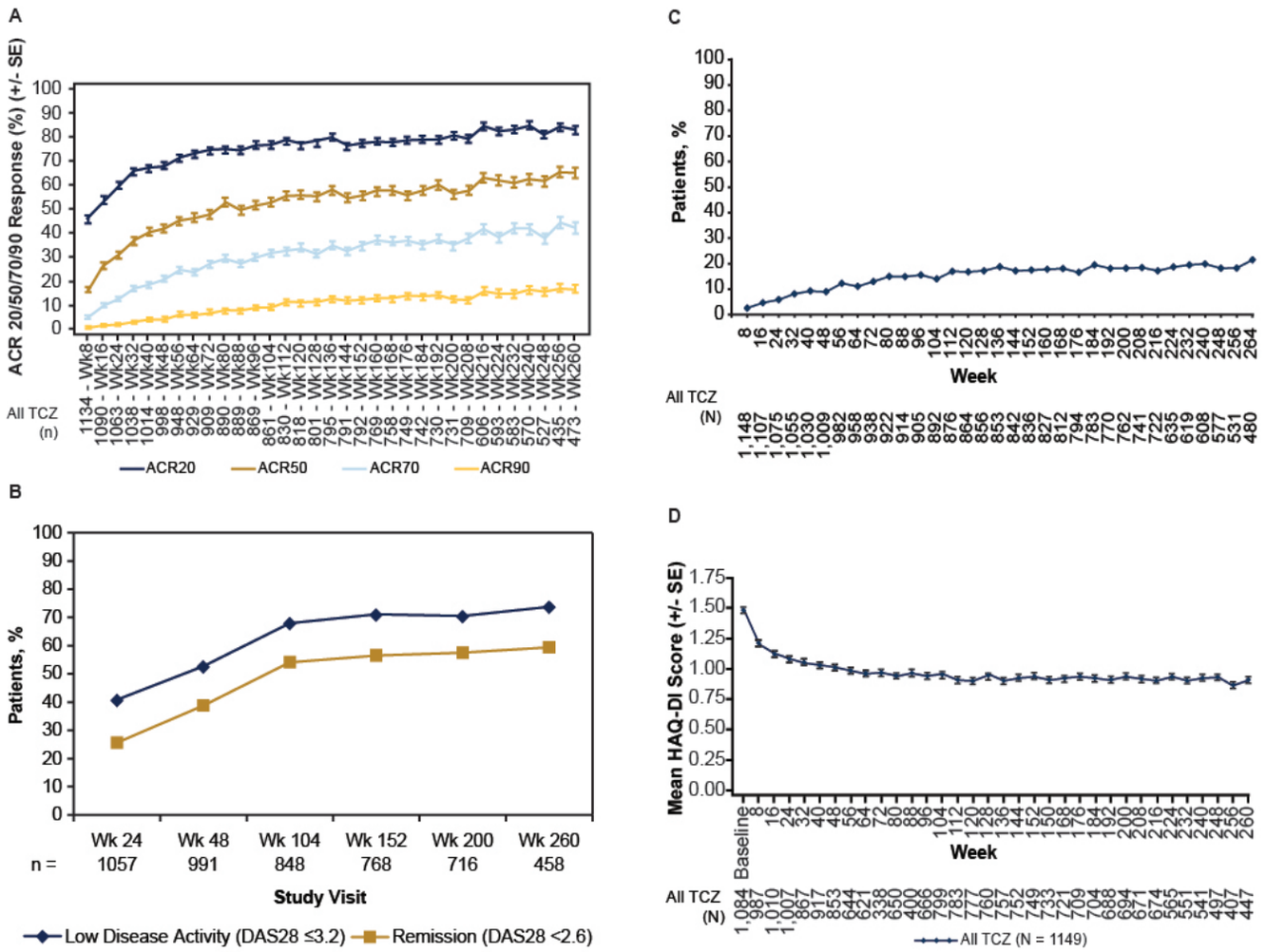


Fig. 2. Signs and symptoms analysis. Maintenance of (**A**) ACR20/50/70/90 response rates, (**B**) DAS28-ESR ≤3.2 and DAS28-ESR <2.6 rates and (**C**) Boolean remission rates. (**D**) Mean HAQ-DI scores over time (tocilizumab population). ACR: American College of Rheumatology; DAS28: Disease Activity Score at 28 joints; ESR: erythrocyte sedimentation rate; HAQ-DI: Health Assessment Questionnaire–Disability Index; SE: standard error; TCZ: tocilizumab.

the overall rates of AEs, serious AEs (SAEs) or AEs requiring dose interruption (Table I). Overall, 94.1% of patients experienced ≥1 AE, and 27.4% reported SAEs (Supplementary Fig. S5). The overall AE rate was highest during year 1 (331.8/100 PY); the rate decreased and then remained stable from year 2 onward. Consistent with AEs reported in years 1 and 2, the most common AEs after 260 weeks were upper respiratory tract infections (12.3/100 PY), urinary tract infections (7.4/100 PY) and bronchitis (6.1/100 PY); most AEs were mild or moderate. The overall SAE rate was 11.7/100 PY. The most frequently reported SAEs in years 3–5 were infection (3.4/100 PY), injury, poisoning and procedural complications (0.98/100 PY) and neoplasms (1.0/100 PY). Rates of the most common SAEs by system organ class are shown in Table II. Overall, 240 patients experienced 240 AEs that led to study withdrawal (5.48/100 PY). The incidence of AEs leading to withdrawal was highest during the first 12 months (10.2/100 PY) and decreased steadily over time to 3.1/100 PY at the >48-month follow-up. Twenty-two patients died (10 during years 1–2, 12 during years 3–5; causes are shown in Supplementary Table S2). Eleven pregnancies were reported in nine patients while they received tocilizumab + MTX (rate = 0.25/100 PY); four resulted in normal delivery, two in therapeutic abortion and one in miscarriage, and four were lost to follow-up.

The overall rate of serious infections was 3.42/100 PY, with pneumonia and cellulitis the most common. The rate of serious infections was stable over the 5-year period. Serious infections were generally not associated with neutropenia; only one patient had a serious infection (empyema) in association with grade 3 neutropenia within 30 days before infection. The overall opportunistic infection rate was 0.27/100 PY (12 events in 12 patients). This rate remained stable over time, and no event was fatal. Events included gastrointestinal fungal infection and oesophageal candidiasis (two patients each; 0.05/100 PY), *Candida* osteomyelitis, gastrointestinal candidiasis, coccidioidomycosis, genital herpes zoster, *Mycobacterium avium* complex and *Mycobacterium chelonae* infection, cryptococcal pneumonia and systemic *Candida* (one patient each; 0.02/100 PY).

Twelve SAEs (0.27/100 PY) occurred during or within 24 hours of infusion.

Table I. AE rates/100 PY by 12-month periods (tocilizumab population).

AE Category	Overall	Months				
		0-12	13-24	25-36	37-48	>48
Total exposure (PY)	4379.6	1014.6	900.7	807.0	746.8	910.6
Patients with ≥1 AE, n (%)	1081 (94.1)	893 (77.7)	739 (64.3)	628 (54.7)	562 (48.9)	538 (46.8)
AEs						
Total number of AEs	10,864	3366	2285	1891	1600	1695
Per 100 PY	248.1	331.8	253.7	234.3	214.3	186.2
95% CI for rate	243.4, 252.8	320.7, 343.2	243.4, 264.3	223.9, 245.1	203.9, 225.0	177.4, 195.2
SAEs						
Total number of SAEs	511	132	91	94	98	95
Per 100 PY	11.7	13.0	10.1	11.7	13.1	10.4
95% CI for rate	10.7, 12.7	10.9, 15.4	8.1, 12.4	9.4, 14.3	10.7, 16.0	8.4, 12.8
All infections						
Patients with ≥1 AE	872	551	431	405	340	355
Per 100 PY	19.9	54.3	47.9	50.2	45.5	39.0
95% CI for rate	18.6, 21.3	49.9, 59.0	43.4, 52.6	45.4, 55.3	40.8, 50.6	35.0, 43.3
Serious infections						
Patients with ≥1 AE	114	33	22	25	27	25
Per 100 PY	2.6	3.3	2.4	3.1	3.6	2.7
95% CI for rate	2.1, 3.1	2.2, 4.6	1.5, 3.7	2.0, 4.6	2.4, 5.3	1.8, 4.1
Malignancies						
Total number of AEs	40	12	4	5	10	9
Per 100 PY	0.91	1.18	0.44	0.62	1.34	0.99
95% CI for rate	0.7, 1.2	0.6, 2.1	0.1, 1.1	0.2, 1.5	0.6, 2.5	0.5, 1.9

PY refers to duration in the study, calculated from the first intake of active drug to the last safety assessment available + 1 day. Month is equivalent to 28 days. Multiple occurrences of the same AE in a patient are counted. AE: adverse event; CI: confidence interval; PY: patient-years; SAEs: serious adverse events.

These included two events each of anaphylactic shock and anaphylactic reaction and one event each of cellulitis, salpingitis, upper respiratory infection, tubo-ovarian abscess, anaemia, mouth ulceration, syncope and infusion site reaction.

Patients were screened for anti-tocilizumab antibodies. Sixteen patients (1.4%) had positive results using the confirmation assay; four of these 16 patients experienced anaphylactic reaction during year 1 (Suppl. Fig. S6).

Malignancy rates varied in each time period, but 95% confidence intervals overlapped with no obvious trend or unusual increase in any type over time (data not shown). There were 54 confirmed malignancies, including 19 non-melanoma skin cancer (NMSC) and two unknown status (overall rate, 1.23/100 PY). The 19 NMSCs included 10 basal cell carcinomas in nine patients and nine squamous cell carcinomas in five patients. Of the 35 non-NMSC malignancies, the most common were prostate cancer, breast cancer and lung adenocarcinoma; these occurred in four patients each (0.09/100 PY).

Serious cardiac disorders were reported at a rate of <1.5/100 PY. The overall myocardial infarction rate was 0.16/100 PY, and rates did not increase over time; six patients experienced seven events, but none were fatal. The overall rate of stroke (ischaemic, haemorrhagic and transient ischaemic attacks) was 0.46/100 PY (20 events in 18 patients); no particular pattern was identified regarding the timing of events. Two cases were fatal.

No notable changes in red blood cell count, hematocrit, lymphocyte count and monocyte or eosinophil count were observed through year 5. The overall rate of serious bleeding events was 0.23/100 PY (10 events in 10 patients) and remained stable over time. These included bleeding in the gastrointestinal tract (two patients) and fatal subarachnoid haemorrhage (one patient; congenital brain aneurysm was described as a possible cause of the event). No bleeding events occurred in patients with grade 3/4 thrombocytopenia.

The highest Common Toxicity Criteria grade for thrombocytopenia was grade 1 for 226 patients (19.7%), grade 2 for 12 patients (1.0%), grade 3 for five patients (<1%) and grade 4 for two patients (<1%). Approximately 90% of patients had a normal platelet count in any 12-month period. Less than 1% of patients had grade 2, 3 or 4 reductions in platelet counts in any 12-month period. There was no evidence of individual platelet counts continuing to drop over time. Sixty-six patients experienced grade 3 or 4 neutropenia; five reported neutropenia at ≥3 consecutive visits. Of seven patients who were discontinued because of neutropenia, none reported serious infection.

Increased ALT/AST levels from normal at baseline to above the upper limit of normal (ULN) at any time during follow-up were reported in 73.7%/64.7% of patients; most shifts occurred from normal at baseline to worst value >1-3× ULN (60.6%/60.1%; Table III). Shifts from normal at baseline to >3-5× ULN and >5× ULN were reported for 10.0% and 3.1%, respectively, in ALT and for 3.7% and 0.9%, respectively, in AST. After years 1 and 2, a steady decline in elevations >ULN occurred. The rate of ALT elevations (grade 3 or 4) was 2.5% in year 1 and <1% in each year for years 2–5. Fourteen patients discontinued as a result of increased ALT levels. Rates of AST elevations (grade 3 or 4) were <1% in each year for years 1–5. No patients discontinued as a result of increased AST levels.

The overall gastrointestinal perforation rate was 0.25/100 PY (11 events in 10 patients). No events were fatal. Four of five patients with medically confirmed serious events were receiving steroids.

Discussion

This report describes the long-term efficacy and safety data collected up to year 5 for all patients who received ≥1 dose of tocilizumab during the LITHE study (tocilizumab population). Results in the first 2 years demonstrated inhibition of radiographic progression and improvements in RA signs and symptoms (14) that were sustained up to 3 years (19). In the current analysis, clinical benefits in all aspects of the disease (joint damage prevention, sign and symptom improvement and physical function improvement) observed

Table II. SAE rates/100 PY by system organ class and 12-month periods (tocilizumab population).

System Organ Class	Overall	Months				
		0-12	13-24	25-36	37-48	>48
Infections and infestations	150 (3.42)	37 (3.65)	24 (2.66)	30 (3.72)	30 (4.02)	29 (3.18)
Injury, poisoning and procedural complication	43 (0.98)	16 (1.58)	8 (0.89)	4 (0.50)	6 (0.80)	9 (0.99)
Neoplasms, benign, malignant and unspecified	45 (1.03)	14 (1.38)	5 (0.56)	7 (0.87)	10 (1.34)	9 (0.99)
GI disorders	31 (0.71)	10 (0.99)	5 (0.56)	7 (0.87)	5 (0.67)	4 (0.44)
Musculoskeletal disorders	34 (0.78)	4 (0.39)	5 (0.56)	11 (1.36)	7 (0.94)	7 (0.77)
Nervous system disorders	33 (0.75)	9 (0.89)	6 (0.67)	5 (0.62)	8 (1.07)	5 (0.55)
Cardiac disorders	36 (0.82)	6 (0.59)	10 (1.11)	6 (0.74)	9 (1.21)	5 (0.55)
Respiratory, thoracic and mediastinal disorders	28 (0.64)	5 (0.49)	6 (0.67)	8 (0.99)	2 (0.27)	7 (0.77)
Vascular disorders	15 (0.34)	4 (0.39)	1 (0.11)	4 (0.50)	2 (0.27)	4 (0.44)
General disorders	15 (0.34)	3 (0.30)	4 (0.44)	2 (0.25)	3 (0.40)	3 (0.33)
Blood and lymphatic system disorders	13 (0.30)	2 (0.20)	4 (0.44)	3 (0.37)	1 (0.13)	3 (0.33)
Hepatobiliary disorders	16 (0.37)	3 (0.30)	3 (0.33)	1 (0.12)	5 (0.67)	4 (0.44)
Renal and urinary disorders	9 (0.21)	3 (0.30)	1 (0.11)	—	3 (0.40)	2 (0.22)
Skin and subcutaneous tissue disorders	8 (0.18)	1 (0.10)	1 (0.11)	—	—	—
Immune system disorders	6 (0.14)	4 (0.39)	2 (0.22)	—	—	—
Metabolic and nutrition disorders	6 (0.14)	2 (0.20)	—	3 (0.37)	1 (0.13)	—
Reproductive system disorders	6 (0.14)	2 (0.20)	2 (0.22)	—	1 (0.13)	1 (0.11)
Eye disorders	4 (0.09)	2 (0.20)	1 (0.11)	—	—	—
Pregnancy, puerperium and perinatal conditions	4 (0.09)	—	2 (0.22)	2 (0.25)	—	—
Endocrine disorders	3 (0.07)	1 (0.10)	1 (0.11)	—	—	1 (0.11)
Investigations	3 (0.07)	2 (0.20)	—	1 (0.12)	—	—
Psychiatric disorders	3 (0.07)	2 (0.20)	—	—	—	1 (0.11)

Data are number of events (rate per 100 PY). PY refers to duration in the study, calculated from the first intake of active drug to the last safety assessment available + 1 day. Month is equivalent to 28 days. Multiple occurrences of the same AE in a patient are counted. AE: adverse event; PY: patient-years; SAE: serious adverse event.

early in the first few months of treatment with tocilizumab + MTX were maintained in the tocilizumab population for up to 260 weeks. Improved physical function, as assessed by mean HAQ-DI scores, was demonstrated, with reductions of up to 0.75 HAQ-DI points maintained over time.

The safety profile during years 3–5 of tocilizumab treatment was consistent with that previously reported for year 2 (14). No increase in the frequency or severity of AEs or laboratory abnormalities and no new safety findings of note occurred. These findings support the relative efficacy and safety of long-term tocilizumab treatment. Tolerability was maintained over the extension period, with the incidence of withdrawals during years 3–5 generally similar at each 24-week time point and lower than reported during the first three 24-week periods.

The current radiographic findings may have clinical implications for patients treated with tocilizumab. In particular, the smaller change in JSN that occurred in patients initially assigned to tocilizumab may indicate greater preservation of physical function given that cartilage damage has been associated with physical disability (20). Because joint damage progression is irreversible, APRs in patients switched from placebo to tocilizumab did not 'catch up' to those observed in patients initially assigned to tocilizumab, thus demonstrating a benefit of earlier intervention. Radiographic progression was minimal in patients who received tocilizumab throughout the trial and in patients who switched from placebo to tocilizumab. No radiographic progression over 5 years was reported by 53% of patients originally assigned to tocilizumab + MTX and by 35% who originally received placebo + MTX and switched to tocilizumab + MTX. Only patients who received tocilizumab in year 3 were included in the current radiographic analysis, excluding patients who withdrew before year 2. As such, direct comparisons should not be made with earlier published data (13, 14), and extrapolation of the 5-year results to earlier time points is not feasible. Few studies have been published that

Table III. Shifts in ALT *vs*. AST (tocilizumab population) to last follow-up (median, 4.69 years).

Baseline value	Worst value to last follow-up, n (%)			
	Normal	>1× ULN-3× ULN	>3× ULN-5× ULN	>5× ULN
ALT (N = 1149)				
Normal	214 (18.6)	696 (60.6)	115 (10.0)	36 (3.1)
>ULN-3× ULN	2 (<1)	50 (4.4)	25 (2.2)	10 (<1)
>3× ULN-5× ULN	0	0	0	1 (<1)
>5× ULN	0	0	0	0
AST (N = 1149)				
Normal	364 (31.7)	690 (60.1)	43 (3.7)	10 (<1)
>ULN-3× ULN	0	30 (2.6)	8 (<1)	3 (<1)
>3× ULN-5× ULN	0	1 (<1)	0	0
>5× ULN	0	0	0	0

ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal. AST ULN = 40 U/L; ALT ULN = 55 U/L.

include radiographic data for other biologic agents for the treatment of RA patients over 5 years. In the completers cohort of the PREMIER study, 53% of adalimumab + MTX patients, 34% of adalimumab patients and 33% of MTX patients experienced no radiographic progression after 5 years (21). In the open-label extension of the AIM study, 45% of patients treated with abatacept (with or without MTX) had no radiographic progression at year 5 (22). Although results appear similar to those of the current study, differences in study design between open-label long-term extensions make direct comparison challenging. The dose of tocilizumab received by almost all patients was 8 mg/kg. Although it was not investigated in the current study, tocilizumab dose reduction from 8 mg/kg to 4 mg/kg in a retrospective proof-of-principle study in 22 RA patients was found to be feasible in patients who had maintained low disease activity (DAS28 <3.2) (23). Whether tocilizumab dose reduction is possible in patients who maintain efficacy over 5 years warrants examination in future studies.

Limitations of the current study included an increased likelihood that patients with insufficient responses would withdraw earlier, indicating that the study population was enriched for good responders who continued for up to 5 years. Radiographic data were assessed conservatively in that patients were analysed in their initial randomisation groups; however, most patients in the placebo group had received tocilizumab therapy for ≥12 months by year 3. Nonetheless, the demographics of patients who entered the long-term extension were similar to those of the overall study population, and the inhibition of joint damage progression remained greater in patients originally assigned to tocilizumab through year 5, supporting the applicability of the long-term efficacy and safety of tocilizumab to the general RA population. The current findings may be limited by the stringent inclusion and exclusion criteria of a clinical trial setting. Recent real-world findings have shown comparable clinical outcomes in patients treated with tocilizumab (24), though the results were in patients with long-standing RA who were inadequate responders to tumour necrosis factor inhibitors and who were treated with tocilizumab for up to 6 months. Longer-term studies are needed to confirm the current findings in the real-world setting. Mean DAS28-ESR at 6 months was 3.7 in the tocilizumab population; 40.8% of patients had DAS28-ESR ≤3.2. According to EULAR guidelines, treatment should be adjusted for patients who do not achieve DAS28 ≤3.2 by 6 months (25). The current study was initiated in 2004, when the guidelines were still in development. Therefore, the study design did not mandate withdrawal if DAS28-ESR ≤3.2 was not achieved by 6 months. Another limitation is that the study was not designed or powered for statistical analysis because there was no appropriate control group at year 5, precluding any statistical comparisons of the 5-year data by originally assigned treatment.

In conclusion, this study confirms the long-term efficacy and safety profile of tocilizumab in patients with moderate to severe RA who previously experienced inadequate responses to MTX.

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