Tocilizumab Inhibits Structural Joint Damage and Improves Physical Function in Patients with Rheumatoid Arthritis and Inadequate Responses to Methotrexate: LITHE Study 2-year Results

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ABSTRACT. ***Objective.*** To assess radiographic progression, physical function, clinical disease activity, and safety in patients with rheumatoid arthritis (RA) who had inadequate response to methotrexate (MTX) and who were treated with tocilizumab-MTX or MTX during Year 2 of a 2-year study.

Methods. During Year 1, patients were randomized to placebo-MTX, 4 mg/kg tocilizumab-MTX, or 8 mg/kg tocilizumab-MTX. During Year 2, patients continued the initial double-blind treatment or switched to open-label 8 mg/kg tocilizumab-MTX. Co-primary endpoints at Week 104 were mean change from baseline in Genant-modified Total Sharp Score (GmTSS) and adjusted mean area under the curve (AUC) for change from baseline in the Health Assessment Questionnaire–Disability Index (HAQ-DI). Signs and symptoms of RA and safety were also evaluated.

Results. At Week 104, mean change from baseline in GmTSS was significantly lower for patients initially randomized to tocilizumab-MTX 4 mg/kg (0.58; $p = 0.0025$) or 8 mg/kg (0.37; $p < 0.0001$) than for patients initially randomized to placebo-MTX (1.96). Adjusted mean AUC of change from baseline in HAQ-DI was also significantly lower in patients initially randomized to tocilizumab-MTX 4 mg/kg (–287.5; $p < 0.0001$) or 8 mg/kg (–320.8; $p < 0.0001$) than in patients initially randomized to placebo-MTX (–139.4). Signs and symptoms of RA were maintained or showed improvement. No new safety signals were noted.

Conclusion. Compared with placebo-MTX, tocilizumab-MTX significantly inhibited structural joint damage and improved physical function in patients with RA who previously had inadequate response to MTX. An extension of this study is continuing and will provide additional longterm efficacy and safety data. National Clinical Trials registry NCT00106535. (First Release Jan 15 2013; J Rheumatol 2013;40:113–26; doi:10.3899/jrheum.120447)

Key Indexing Terms:
RHEUMATOID ARTHRITIS
INTERLEUKINS
BIOLOGICAL PRODUCTS
RANDOMIZED CONTROL TRIAL

Tocilizumab is a humanized monoclonal antibody that inhibits interleukin 6 (IL-6) binding to soluble and membrane-expressed IL-6 receptors, therefore blocking IL-6 receptor signaling and subsequent proinflammatory activities[1,2,3]. Seven phase III clinical trials evaluated the efficacy and safety of tocilizumab, given as monotherapy or in combination with methotrexate (MTX) or other disease-modifying antirheumatic drugs (DMARD), in patients with moderate to severe rheumatoid arthritis (RA)[4,5,6,7,8,9,10]. Data from these trials show that tocilizumab reduces signs

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Supported by F. Hoffmann-La Roche Ltd. R.M. Fleischmann has received research grants and consulting fees, speaking fees, and/or honoraria from Abbott, Amgen, Janssen, UCB, BMS, Roche, Genentech, Lexicon, Sanofi-Aventis, Lilly, MSD, Pfizer, and Regeneron. A. Halland has received honoraria from Roche and Abbott (less than $10,000). M. Brzosko has received lecture/instructor fees from Roche, Abbott, Amgen, Pfizer, MSD, Novartis, Schering-Plough, and Sanofi-Aventis. R. Burgos-Vargas has received research grants from Roche and consulting fees and speakers fees from Abbott, BMS, MSD, Roche, and UCB. J.M. Kremer has received research grants from Abbott, BMS, Genentech, Janssen, Pfizer, and UCB and is on the speakers bureau for Abbott, BMS, and Genentech

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Accepted for publication October 19, 2012.

and symptoms of RA, inhibits radiographic progression, and improves patient function[4,5,6,7,8,9,10]. The safety profile of tocilizumab was consistent among the studies and was associated with a risk-benefit ratio that supported its use in patients with RA[4,5,6,7,8,9,10].

The tociLIzumab Safety and THE Prevention of Structural Joint Damage (LITHE) study was a 2-year trial that assessed radiographic progression, physical function, clinical disease activity, and safety in patients with RA who had inadequate response to MTX and were treated with tocilizumab plus MTX or MTX alone. The 1-year (Week 52) interim analysis of the double-blind placebo-controlled treatment phase of the LITHE study demonstrated that tocilizumab (4 or 8 mg/kg) plus MTX was statistically better than MTX monotherapy regarding inhibition of radiographic progression and improvement in physical function[11]. The objective of the 2-year (Week 104) analysis of the open-label phase of the LITHE study was to evaluate the maintenance of these effects. (A full list of LITHE investigators is published elsewhere[12].)

We report the radiographic progression, physical function change, clinical efficacy, and safety profile from Year 2 of the LITHE study. Because most patients received 8 mg/kg tocilizumab during Year 2, patients receiving this dose are the primary focus of the report.

MATERIALS AND METHODS

Study design. The LITHE study is a randomized, 3-arm, placebo-controlled, parallel-group, multicenter phase III trial in patients with moderate to severe active RA and inadequate response to MTX. Patients who participated in Year 2 of the LITHE study continued their initial double-blind treatment or switched to open-label tocilizumab 8 mg/kg plus MTX therapy (Figure 1). After Year 2, patients could participate in an ongoing, optional, open-label extension phase during Years 3 to 5.

Study population. Inclusion and exclusion criteria were previously reported[11]. Briefly, eligible patients had RA (moderate to severe in the investigators' opinions) according to 1987 American College of Rheumatology (ACR) criteria for ≥ 6 months and inadequate response to MTX for at least 12 weeks before baseline (stable at 10–25 mg/wk for ≥ 8 weeks). Inadequate response was defined as swollen joint count (SJC) ≥ 6, tender joint count (TJC) ≥ 8, and either C-reactive protein (CRP) ≥ 1 mg/dl or erythrocyte sedimentation rate (ESR) ≥ 28 mm/h. Patients must have had ≥ 1 centrally read, radiographically confirmed joint erosion to be eligible for study participation. Ethical considerations and compliance were as reported[11].

Treatment. Randomization was stratified by site. Patients received intravenous infusions of 4 or 8 mg/kg tocilizumab or placebo (1:1:1) every 4 weeks in combination with their stable dose of MTX, referred to as 4 mg/kg tocilizumab-MTX, 8 mg/kg tocilizumab-MTX, and placebo-MTX, respectively. Oral corticosteroids (≤ 10 mg/day prednisone equivalent) and nonsteroidal antiinflammatory drugs were permitted if doses were stable for ≥ 6 weeks before study entry.

All patients received ≥ 5 mg/wk folic acid. Beginning at treatment Week 16, and up to treatment Week 52, patients could receive rescue therapy if they did not achieve ≥ 20% improvement from baseline in SJC and TJC. Patients in the placebo-MTX group received 4 mg/kg tocilizumab-MTX in a blinded fashion and patients in the 4 mg/kg tocilizumab-MTX and 8 mg/kg tocilizumab-MTX groups received 8 mg/kg tocilizumab-MTX as first-step rescue therapy; steroids were provided if needed. If an inadequate response (defined above) persisted after 3 doses of first-step rescue therapy, patients were advanced to second-step rescue therapy, which consisted of 8 mg/kg tocilizumab-MTX through Week 52. Patients who did not respond after 3 doses of second-step rescue discontinued treatment.

At the beginning of Year 2, patients who attained ≥ 70% improvement from baseline in SJC and TJC at 2 consecutive visits during Year 1 were allowed to continue double-blind treatment during Year 2 at the discretion of either the patient or the investigator; all others received open-label treatment with 8 mg/kg tocilizumab-MTX every 4 weeks (Figure 1).

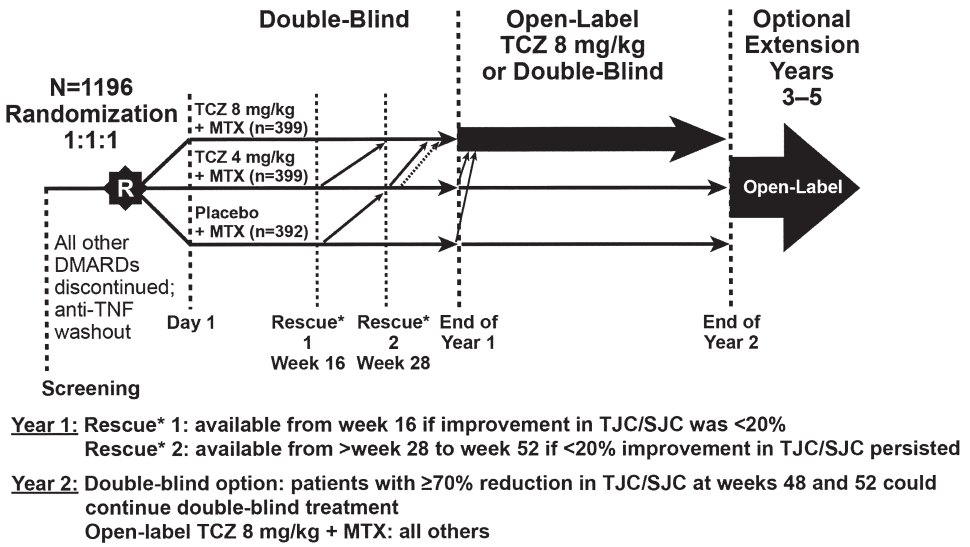


Figure 1. The design of the study. Placebo patients who received rescue 1 (with tocilizumab 4 mg/kg) could receive rescue 2 (with tocilizumab 8 mg/kg) if required. *Patients could receive rescue at any point between Week 16 and the end of Year 1. DMARD: disease-modifying antirheumatic drugs; MTX: methotrexate; SJC: swollen joint count; TCZ: tocilizumab; TJC: tender joint count; TNF: tumor necrosis factor.

Patients who chose to continue double-blind therapy during Year 2 were permitted to switch to open-label tocilizumab-MTX 8 mg/kg at any time.

Study endpoints. Co-primary endpoints at Week 104 were change from baseline in Genant-modified Total Sharp Score (GmTSS)[13] and change in physical function as measured by area under the curve (AUC) for change from baseline in the Health Assessment Questionnaire–Disability Index (HAQ-DI)[14].

Secondary endpoints included change in erosion and joint space narrowing (JSN) scores, annualized progression rate (an estimated value), proportion of patients with no progression of GmTSS score (≤ 0 change in GmTSS), ACR20/50/70 response[15], major clinical response (ACR70 for 24 weeks), change in ACR core components (including SJC, TJC, and HAQ-DI over time), Disease Activity Score using 28 joints (DAS28-ESR)[16], DAS28 < 2.6, DAS28 ≤ 3.2, and European League Against Rheumatism (EULAR) response at Week 104. CRP data were used for ACR calculations; if CRP data were missing, ESR data were used.

Assessments. Clinical efficacy assessments were performed every 4 weeks; radiographs of the hands and feet were obtained at Weeks 0, 24, 52, 80, and 104. Radiographs were independently read by 2 radiologists using the GmTSS[17] at a central reading facility that used a proprietary image scoring system (SynaVu; Synarc) customized for evaluation of RA. The radiographic reading campaign in Year 2 was independent of the reading campaign in Year 1. Reading campaign 2 comprised evaluations at baseline; Weeks 24, 52, 80, and 104; and early withdraw/rescue readings taken up to the Week 104 visit. Readers were blinded to treatment assignment and sequence; mean change of the 2 assessors' readings was calculated. Consistency in scoring was ensured by having the assessors participate in training and validation sessions before they assessed patient data.

Safety evaluations included assessment of adverse events (AE), clinical laboratory tests (hematology, blood chemistry, lipid panel, urinalysis), and physical examination findings. Patients who withdrew early underwent followup safety assessments (vital signs, concomitant medications, AE monitoring, clinical laboratory tests) at 4, 8, and 12 weeks after discontinuing study treatment. Study treatment was interrupted in patients with alanine transaminase (ALT) or aspartate transaminase (AST) values ≥ 3 times the upper limit of normal (ULN) and was resumed once levels were < 3 times ULN. Treatment was discontinued if ALT or AST elevation ≥ 3 times ULN was accompanied by total bilirubin > 2 times ULN, international normalized ratio > 1.5, liver alkaline phosphatase > 2 times ULN, absolute neutrophil count < 0.5×10^9/l (normal range, 4–6×10^9/l)[18], or worsening fatigue, nausea, vomiting, fever, rash, or eosinophilia.

Statistical analyses. Calculation of sample size was based on the number of patients needed to show prevention of joint destruction at 12 months. An estimated 390 patients per treatment arm were needed to provide 90% power to detect a statistically significant difference in GmTSS changes between tocilizumab-MTX and MTX alone. The estimation was based on an assumed difference in radiographic score change of about 30% of the standard deviation at 12 months (e.g., a mean difference of 3 units with an SD of 11 units; however, any similar ratio of mean difference to SD gives the same sample size estimate)[17,19,20]. This sample size provided some protection against diminished treatment effects arising from patient withdrawal and data imputation. Because of multiple active treatment arms and time points, an alpha of 0.0125 was used for sample sizing.

Primary endpoint analyses were conducted on all patients in the intent-to-treat (ITT) population, which comprised all randomized patients who received ≥ 1 dose of study medication. To be included in the primary analysis, patients had to have 1 post-Week 52 radiograph. Sensitivity analyses were based on the per-protocol population, which comprised all patients in the ITT population who completed the study without major violation of study entry criteria or postrandomization protocol procedures. The safety population included all randomized patients who received ≥ 1 dose of study medication and who had at least 1 postrandomization safety assessment.

Patients were grouped according to the 3 initially randomized treatment arms, and comparisons were made between each tocilizumab group and the placebo group. For the first co-primary endpoint (change from baseline in GmTSS), the primary analysis was between the 8 mg/kg tocilizumab-MTX and placebo-MTX groups; the 4 mg/kg tocilizumab-MTX and placebo-MTX groups were also compared. Detailed descriptions of data analyses and calculations are provided in figure and table legends where appropriate. The primary statistical analysis was nonparametric (van Elteren test), with region as a stratifying factor and result expressed as a p value. The primary method for handling missing radiographic data was linear extrapolation to impute missing data from Week 52, 80, or 104 for GmTSS, erosion score, and JSN score and for patients who received rescue therapy or withdrew and underwent postwithdrawal radiograph. Linear extrapolation was performed for all patients who underwent baseline assessment and ≥ 1 postbaseline radiographic assessment before or on the day of the switch to rescue therapy or withdrawal. Descriptive statistics are provided for the observed values at baseline and Week 104 and the change from baseline at Week 104 for GmTSS. The term "no progression" in GmTSS was conservatively defined using 0 as the cutoff because no consensus exists on a standard definition.

For AUC of change from baseline in HAQ-DI, analysis of variance adjusted for region and original treatment group on the ITT population was used. Data for rescue or early withdrawal patients was set to missing at the time of rescue or withdrawal. For patients with missing Week 104 HAQ-DI scores, AUC of change from baseline was standardized to 104 weeks using the latest timepoint available for calculation of the AUC.

Patients who switched to rescue therapy or who withdrew were classified as nonresponders for ACR20/50/70 response. For DAS28-ESR, patient data were set to missing and were not included in the analysis; low disease activity state (LDAS) and DAS28 < 2.6 were then categorized on those data. P values were not calculated for secondary endpoints because at the end of Year 2 most patients had been receiving active treatment for a long time.

Sensitivity analyses were conducted for radiographic endpoints and change from baseline in HAQ-DI. For GmTSS, sensitivity analyses were performed by repeating analyses on the per-protocol population. A time window of ± 30 days was applied to the GmTSS at Weeks 52 and 104. If no GmTSS fell within this ± 30-day window at Week 52 or 104, data were imputed using linear extrapolation. Further sensitivity analyses on radiographic endpoints were performed on the ITT population by including all data collected during rescue therapy or after withdrawal. For AUC of the change from baseline in HAQ-DI, sensitivity analyses were performed on the ITT population using the last-observation-carried-forward method.

The safety profile of 4 mg/kg tocilizumab-MTX and 8 mg/kg tocilizumab-MTX compared with placebo-MTX was based on the Year 1 analysis, in which treatment groups could be compared directly. Patients were expected to switch to open-label treatment with 8 mg/kg tocilizumab-MTX during the second year; therefore, a cumulative analysis up to Week 104 was planned. Thus, to allow cumulative analysis of all safety data up to Week 104, safety data were analyzed according to the treatment actually received rather than the treatment to which patients were originally randomized. Cumulative analysis up to Week 104 included post-escape safety data from Year 1 in addition to the new safety data accrued in Year 2. The main goals were to evaluate the effect of an additional year of exposure in patients treated with 8 mg/kg tocilizumab-MTX. Analyses were conducted on all randomized patients who received ≥ 1 dose of study medication and who had ≥ 1 postrandomization safety assessment. AE are presented according to treatment taken at the start of the AE: placebo-MTX, 4 mg/kg tocilizumab-MTX, and 8 mg/kg tocilizumab-MTX. Clinical laboratory data are presented by treatment path: placebo-MTX, 4 mg/kg tocilizumab-MTX, 8 mg/kg tocilizumab-MTX, tocilizumab (4–8 mg/kg)/tocilizumab 4 mg/kg, and tocilizumab (4–8 mg/kg)/tocilizumab 8 mg/kg.

RESULTS

Patient disposition. The ITT patient population comprised

392 patients initially randomized to placebo-MTX, 399 initially randomized to 4 mg/kg tocilizumab-MTX, and 399 initially randomized to 8 mg/kg tocilizumab-MTX (Appendix 1). At Week 52, by protocol design, most patients remaining in the study began open-label treatment with 8 mg/kg tocilizumab-MTX, including 68% of the patients initially randomized to placebo-MTX, 63% initially randomized to 4 mg/kg tocilizumab-MTX, and 62% initially randomized to 8 mg/kg tocilizumab-MTX; the remainder had withdrawn or had not required rescue 8 mg/kg tocilizumab per protocol. Proportions of patients who maintained ≥ 70% improvement in SJC/TJC and continued double-blind treatment were 15%, 22%, and 23%, respectively.

At the end of Year 2, 287 (73%), 310 (78%), and 311 (78%) patients initially randomized to placebo-MTX, 4 mg/kg tocilizumab-MTX, and 8 mg/kg tocilizumab-MTX, respectively, completed treatment. Most patients (248, 269, and 260, respectively) received open-label treatment with 8 mg/kg tocilizumab-MTX; 22, 38, and 49 patients, respectively, were still receiving the treatment to which they were initially randomized during the double-blind portion of the study (Figure 1).

Patient demographics and RA characteristics. Patients were predominantly women (82%–84%); mean age was about 52 years. Treatment groups were well balanced for weight (72.1–73.8 kg), race (Hispanic, 34%–36%), and current smoking (16%–19%). Mean duration of RA was about 9 years, and mean baseline DAS28-ESR score was about 6.5. No meaningful differences at baseline were evident in GmTSS (range 25.25–25.46) or estimated annualized progression rate (range 4.09–4.31).

Inhibition of radiographic progression. The primary analysis, which included patients with at least 1 post-Week 52 radiograph and censored post-escape and postwithdrawal data, included radiographic assessments for 75% (294/393) of patients who received placebo-MTX, 86% (343/399) who received 4 mg/kg tocilizumab-MTX, and 89% (353/398) who received 8 mg/kg tocilizumab-MTX (Table 1). Of those patients, 140 in the placebo-MTX group, 231 in the 4 mg/kg tocilizumab-MTX group, and 252 in the 8 mg/kg tocilizumab-MTX group had baseline and Week 104 radiographs and therefore provided observed-change data. The number of patients who had Week 104 results imputed using linear extrapolation included 154, 112, and 101 patients in the placebo-MTX, 4 mg/kg tocilizumab-MTX, and 8 mg/kg tocilizumab-MTX groups, respectively. Data for these patients were imputed because their observed Week 104 data were set to missing (i.e., escape or postwithdrawal data; 95, 49, and 37 patients, respectively) or because they were truly missing (i.e., early withdrawals for patients with no postwithdrawal data) at Week 104 (59, 63, and 64 patients, respectively).

Mean change from baseline in GmTSS (potential range 0–290) — the co-primary endpoint — was significantly lower for patients initially randomized to 4 mg/kg tocilizumab-MTX (0.58; $p = 0.0025$) and 8 mg/kg tocilizumab-MTX (0.37; $p < 0.0001$) than for patients initially randomized to placebo-MTX (1.96; Figure 2A). Virtually all radiographic progression in the placebo-MTX group occurred during Year 1 (Figure 2B). Sensitivity analyses, including radiographic data from patients obtained after they withdrew or received rescue therapy, confirmed that GmTSS was significantly lower in the 4 mg/kg tocilizumab-MTX (0.47; $p < 0.0001$) and 8 mg/kg tocilizumab-MTX (0.34; $p < 0.0001$) groups than the placebo-MTX group (1.07). As expected, statistically significant reductions in erosion and JSN scores (Figure 2A) also occurred in the tocilizumab-MTX groups.

A cumulative distribution plot of change from baseline at Week 104 in GmTSS using linear extrapolation showed a shift to the right for the curves represented by patients who were initially randomized to 4 mg/kg tocilizumab-MTX or 8 mg/kg tocilizumab-MTX, which indicates greater inhibition of structural joint damage compared with the curve represented by patients who received placebo-MTX (Figure 2C).

Table 1. Radiographic data for primary analysis (intent-to-treat population).

Group	Placebo-MTX, n = 393	4 mg/kg Tocilizumab-MTX, n = 399	8 mg/kg Tocilizumab-MTX, n = 398
Patients with Week 104 radiograph	140	231	252
Patients with Week 104 radiographic data imputed using linear extrapolation	154	112	101
Escape or withdrawal*	95	49	37
No Week 104 radiograph†	59	63	64
Patients included in the primary endpoint analysis	294	343	353

* For withdrawals, only patients with nonmissing postwithdrawal Week 104 radiographs are included in this count. † Includes withdrawal patients with missing postwithdrawal Week 104 radiographs. MTX: methotrexate.

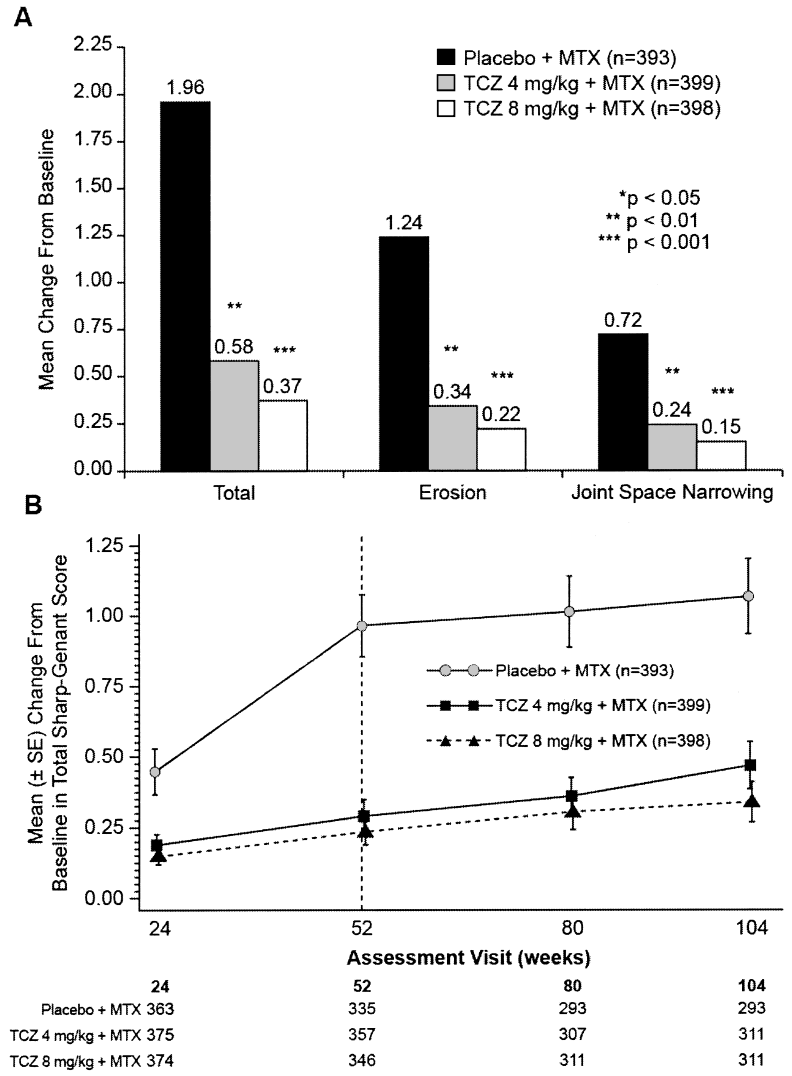


Figure 2. Radiographic efficacy. (A) Mean change from baseline at Week 104 in Genant-modified Total Sharp Score (GmTSS; primary analysis), erosion, and joint space narrowing (JSN) scores [linear extrapolation excluding postwithdrawal/rescue data (intent-to-treat)]. Data collected postwithdrawal/on rescue therapy are excluded. Missing Week 104 radiographic data were imputed using linear extrapolation. Comparisons are to placebo-MTX using van Elteren test stratified by region. Campaign 2 comprises baseline and Week 24, Week 52, Week 80, and Week 104 evaluations. (B) Sensitivity analysis: mean change from baseline by visit to Week 104 in GmTSS [including postwithdrawal/rescue data (intent-to-treat)]. Vertical line at Week 52 indicates scheduled switch to open-label treatment for patients not continuing on double-blind treatment. Data collected postwithdrawal/on escape therapy are included. Linear extrapolation was used for missing data. Campaign 2 comprises evaluations of baseline; Weeks 24, 52, 80, and 104; and early withdrawal/rescue readings taken up to the Week 104 visit. (C) Cumulative distribution of change from baseline at Week 104 in GmTSS. Linear extrapolation excluding withdrawal and escape data (intent-to-treat population). Annualized disease progression rate (APR) year: year in which APR for GmTSS was calculated. MTX: methotrexate; TCZ: tocilizumab.

Overall, and as expected because most patients switched to 8 mg/kg tocilizumab-MTX in Year 2 of the study, the annualized disease progression rate decreased during Year 2, with all treatment groups showing reduced changes in GmTSS (flattened slope), indicating a reduced rate of progression (Figure 2B).

Overall proportions of patients with no progression (≤ 0 change in GmTSS; no imputation for missing data) from Year 1 (Week 52) to Year 2 (Week 104) were 86.8% in the patients initially randomized to the placebo-MTX group, 80.6% to the 4 mg/kg tocilizumab-MTX group, and 93.4% to the 8 mg/kg tocilizumab-MTX group.

As expected, the number of patients who experienced disease progression over 2 years was small; 99 (34%) patients initially randomized to the placebo-MTX group, 87 (25%) initially randomized to the 4 mg/kg tocilizumab-MTX group, and 61 (17%) initially randomized to the 8 mg/kg tocilizumab-MTX group. Among patients with progressive disease, about 60% in each tocilizumab-MTX group compared with about 35% in the placebo-MTX group experienced progression in the ≤ 2 category. Most patients with progressive disease in the 8 mg/kg tocilizumab-MTX group fell into the > 0 to ≤ 0.5 category, whereas most patients with progressive disease in the placebo-MTX group fell into the > 2 to ≤ 5 category. This trend was also observed when nonimputed data were used in the robustness analysis (data not shown).

Clinical measures of RA. Physical function. Physical function, the second co-primary endpoint, improved significantly in patients initially randomized to tocilizumab-MTX. Adjusted mean AUC of change from baseline at Week 104 in HAQ-DI was significantly lower in patients initially randomized to 4 mg/kg tocilizumab-MTX (–287.5; $p < 0.0001$) and 8 mg/kg tocilizumab-MTX (–320.8; $p < 0.0001$) than to placebo-MTX (–139.4). Absolute changes from baseline HAQ-DI scores were 0.95, 0.86, and 0.90 in the placebo-MTX, 4 mg/kg tocilizumab-MTX, and 8 mg/kg tocilizumab-MTX groups, respectively. These scores are lower than those previously observed at Week 52 in all 3 treatment groups (reflecting further improvement). The greatest reduction in score was observed in the placebo-MTX group and may be attributed to a large proportion of patients switching to open-label therapy (8 mg/kg tocilizumab-MTX) during the second year (Figure 3A).

To put these data into clinical context, the numbers of patients who achieved improvement of at least 0.3 units from baseline in the HAQ-DI at Week 104 were summarized. Sixty-two percent of patients initially randomized to 8 mg/kg tocilizumab-MTX achieved improvement of at least 0.3 units from baseline. As expected, similar results were observed for patients randomized to placebo-MTX and 4 mg/kg tocilizumab-MTX because most had switched to open-label 8 mg/kg tocilizumab-MTX at Week 52. Thirty-eight percent of patients randomized to 8 mg/kg tocilizumab-MTX had a HAQ-DI ≤ 0.5 at Week 104; similar results were observed for patients randomized to placebo-MTX and 4 mg/kg tocilizumab-MTX.

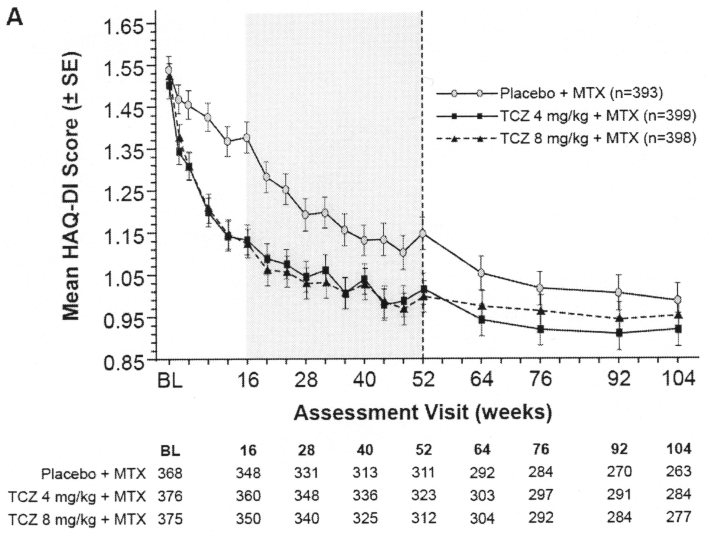
ACR20/50/70 and ACR core set measures. For ACR response, patients who switched to rescue therapy or withdrew were classified as nonresponders. Compared with Year 1 (Week 52), ACR20/50/70 response rates during Year 2 (Week 104) were maintained in patients initially randomized to 8 mg/kg tocilizumab-MTX (55.8%, 36.4%, 20.1% vs 54.5%, 38.9%, 22.4%) and improved in patients initially randomized to placebo-MTX (24.7%, 10.2%, 3.8% vs 29.3%, 19.8%, 12.2%). Major clinical response, defined as ACR70 maintained for 24 weeks, was attained by 14.3% of patients initially randomized to 8 mg/kg tocilizumab-MTX and 5.6% of patients initially randomized to placebo-MTX. SJC and TJC continued to decrease in all 3 groups during Year 2 (Figures 3B, 3C). Change from baseline in ACR core set measures at Week 104 are summarized in Appendix 2.

DAS28-ESR. DAS28-ESR scores continued to decrease during Year 2 in all groups. Patients initially randomized to 8 mg/kg tocilizumab-MTX had the greatest decrease in scores at Week 104 (Figure 4A). When rescue and postwithdrawal data were excluded, more patients initially randomized to 8 mg/kg tocilizumab-MTX than placebo-MTX attained DAS28 < 2.6 (64.7% vs 52.9%; Figure 4B) and DAS28 ≤ 3.2 (76.3% vs 69.1%). Sensitivity analyses that included escape data showed similar trends.

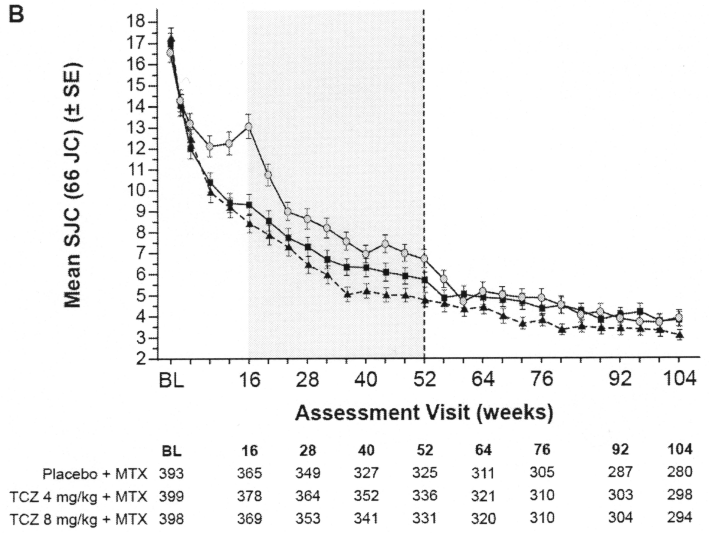
EULAR response. The proportion of patients who achieved good EULAR response during Year 1 was maintained in the 8 mg/kg tocilizumab-MTX group during Year 2 (44.0% vs 45.7%). The proportion of patients who achieved good EULAR response in Year 1 increased in Year 2 (7.1% vs 23.4%) in the group initially randomized to placebo-MTX.

Safety. Overall, rates per 100 patient-years (PY) and nature of AE, severe AE, serious AE (SAE), or AE leading to treatment withdrawal or dose interruption were comparable to those reported during Year 1 of the LITHE study (Table 2)[11].

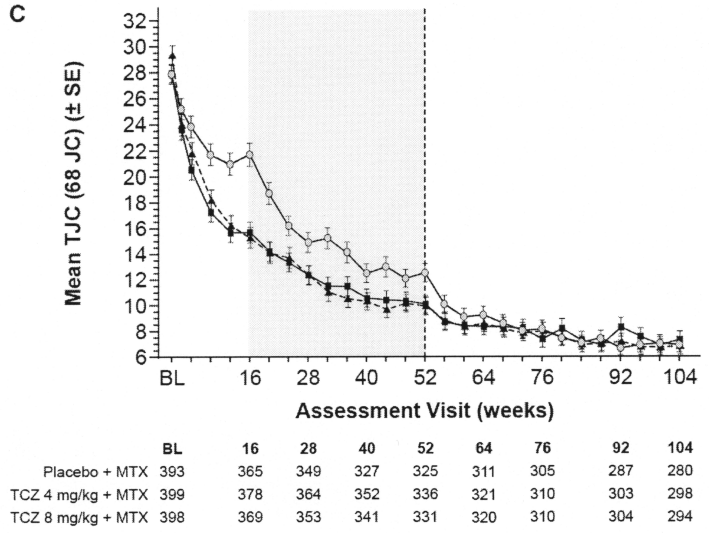
The most frequently reported AE were upper respiratory tract infection, bronchitis, urinary tract infection, hypertension, nasopharyngitis, and increased transaminase levels. The most commonly reported SAE were serious infections (e.g., pneumonia, gastroenteritis, cellulitis; Appendix 3). Overall rates of serious infections were 3.1/100 PY and 3.0/100 PY in the 4 mg/kg and 8 mg/kg tocilizumab-MTX groups, respectively, compared with 2.1/100 PY in the placebo-MTX group. Ten deaths occurred during the 2 years of the study (4 during Year 2 from gastroesophageal cancer, metastatic malignant melanoma, metastatic lung adenocarcinoma, and cardiomyopathy). All 4 patients who died during Year 2 were receiving 8 mg/kg tocilizumab-MTX either as initial therapy or after switching from 4 mg/kg tocilizumab-MTX. AE that most commonly led to treatment



	BL	16	28	40	52	64	76	92	104
Placebo + MTX	368	348	331	313	311	292	284	270	263
TCZ 4 mg/kg + MTX	376	360	348	336	323	303	297	291	284
TCZ 8 mg/kg + MTX	375	350	340	325	312	304	292	284	277



	BL	16	28	40	52	64	76	92	104
Placebo + MTX	393	365	349	327	325	311	305	287	280
TCZ 4 mg/kg + MTX	399	378	364	352	336	321	310	303	298
TCZ 8 mg/kg + MTX	398	369	353	341	331	320	310	304	294



	BL	16	28	40	52	64	76	92	104
Placebo + MTX	393	365	349	327	325	311	305	287	280
TCZ 4 mg/kg + MTX	399	378	364	352	336	321	310	303	298
TCZ 8 mg/kg + MTX	398	369	353	341	331	320	310	304	294

Figure 3. American College of Rheumatology core components. (A) Mean Health Assessment Questionnaire–Disability Index (HAQ-DI) scores by visit up to Week 104 [rescue data included (intent-to-treat; ITT)]. No imputation was used for missing HAQ-DI score. (B) Mean swollen joint count (SJC) by visit up to Week 104 [escape data included (ITT)]. Last-observation-carried-forward for missing data. (C) Mean tender joint count (TJC) by visit up to Week 104 [escape data included (ITT)]. Last-observation-carried-forward for missing data. The vertical reference line at Week 52 indicates the scheduled switch to open-label treatment for patients who did not continue on double-blind treatment. Shading represents the time during which rescue therapy was permitted. BL: baseline; MTX: methotrexate; TCZ: tocilizumab.

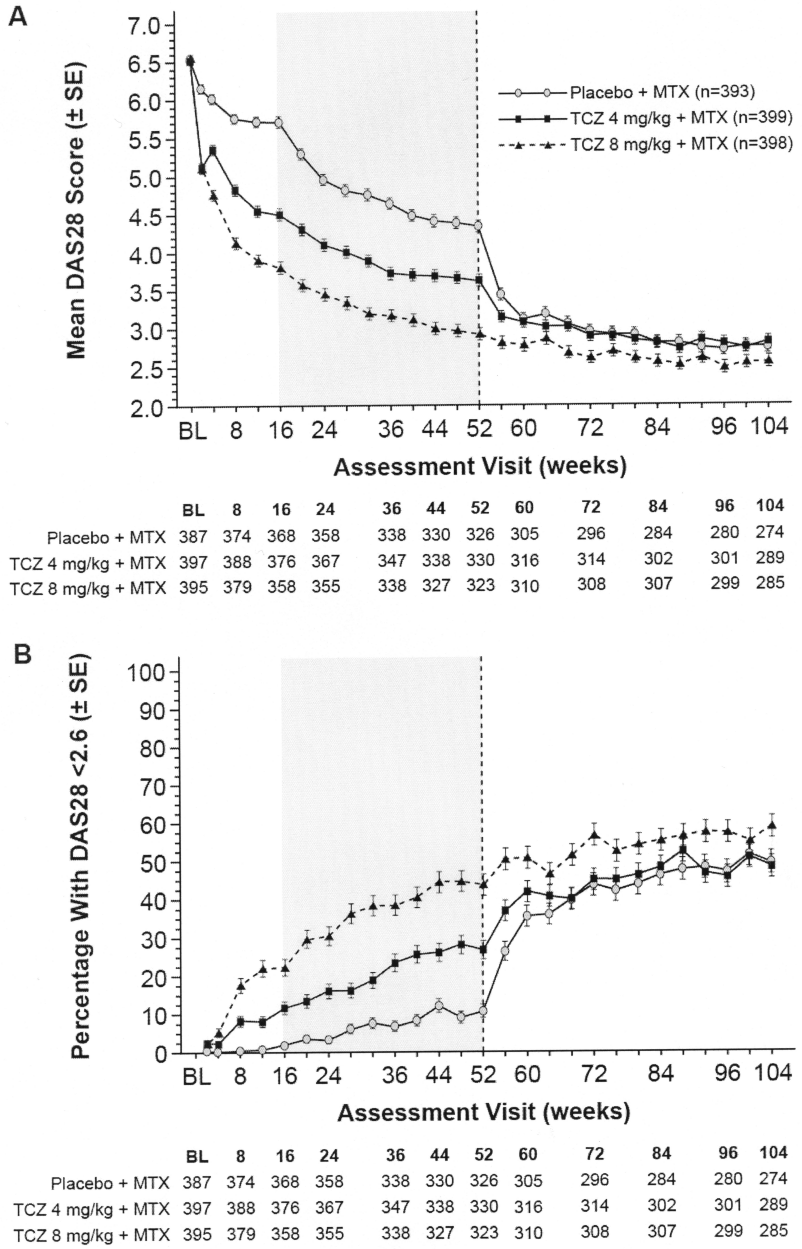


Figure 4. DAS28-ESR scores. (A) Mean DAS28-ESR scores by visit up to Week 104 [rescue data included (ITT)]. (B) Percentage of patients with DAS28 < 2.6 by visit up to Week 104 [escape data included (intent-to-treat)]. The vertical reference line at Week 52 indicates the scheduled switch to open-label treatment for patients who did not continue on double-blind treatment. Shading represents the time during which rescue therapy was permitted. Last-observation-carried-forward was used for SJC and TJC. No imputation was used for ESR and patient global assessment of disease activity. BL: baseline; DAS28: Disease Activity Score in 28 joints; ESR: erythrocyte sedimentation rate; SJC: swollen joint count; TCZ: tocilizumab; TJC: tender joint count.

withdrawal were increased transaminases, infections, and neoplasms.

Laboratory results were consistent with those observed during Year 1[11]. Increases in hepatic measures (ALT, AST, bilirubin) and hemoglobin and initial decreases in absolute neutrophil count were maintained without worsening in similar proportions of patients in Years 1 and 2 (Appendix 4). A similar trend was observed for lipids (total cholesterol, low-density lipoprotein, high-density lipoprotein, triglycerides). In patients who switched from 4 to 8 mg/kg tocilizumab-MTX, most laboratory values were similar to those observed in patients who received only 8 mg/kg

Table 2. Overview of adverse events (AE) pooled by treatment received up to Week 104 (safety population). Multiple occurrences of the same AE in one patient were counted once.

	Placebo-MTX, n = 392	4 mg/kg Tocilizumab-MTX, n = 597*	8 mg/kg Tocilizumab-MTX, n = 983†
Median duration on study, yrs	0.54	0.92	1.08
Total patient-yrs of treatment	284.81	521.90	1320.41
All AE, n (per 100 PY exposure to trial treatment)	716 (251.4)	1439 (275.7)	3481 (263.6)
All serious AE, n (per 100 PY exposure to trial treatment)	31 (10.9)	63 (12.1)	150 (11.4)
AE that led to withdrawal, n (per 100 PY exposure to trial treatment)	12 (4.2)	44 (8.4)	97 (7.3)
AE that led to dose interruption, n (per 100 PY exposure to trial treatment)	58 (20.4)	160 (30.7)	429 (32.5)
Deaths, n†† (per 100 PY exposure to trial treatment)	1 (0.35)	1 (0.19)	8 (0.61)

* Includes 146 non-switch patients and 451 switch patients. † Includes 532 non-switch patients and 451 switch patients. †† Causes of death were Wegener's granulomatosis (placebo); pulmonary embolism (4 mg/kg tocilizumab-MTX); and gastroesophageal cancer, metastatic malignant melanoma, metastatic lung adenocarcinoma, cardiomyopathy, cerebral hemorrhage, gastrointestinal infection, bronchopneumonia, and sepsis (8 mg/kg tocilizumab-MTX). MTX: methotrexate.

tocilizumab-MTX. Prolonged exposure to tocilizumab was not associated with increased frequency or severity of blood chemistry changes.

Four patients had gastrointestinal perforations during the 2 years of the study (2 each in Years 1 and 2). Of the Year 2 gastrointestinal perforations, 1 occurred in a patient who switched from placebo to 4 mg/kg tocilizumab-MTX to 8 mg/kg tocilizumab-MTX and had underlying diverticulitis. The other occurred in a patient with appendicitis who received only 8 mg/kg tocilizumab-MTX during the study.

Malignancy rates were higher in the 4 mg/kg tocilizumab-MTX group (1.92/100 PY; total 521.90 PY) than in the placebo-MTX (0.70/100 PY; total 284.81 PY) or 8 mg/kg tocilizumab-MTX (0.98/100 PY; total 1320.41 PY) group. Twenty-three malignancies were reported in tocilizumab-treated patients up to Week 104; 17 of the 23 were reported within the first 52 weeks of the study. The most commonly reported malignancies were basal cell carcinoma (4 patients) and prostate cancer (2 patients). All other malignancies were reported once (cervix carcinoma stage 0, cervix carcinoma stage III, lung squamous cell carcinoma stage III, endometrial cancer, gastroesophageal cancer, metastatic non-small cell lung cancer, renal cell carcinoma stage I, thyroid cancer, skin cancer, lung neoplasm, metastatic tongue cancer, metastatic malignant melanoma, squamous cell carcinoma of the skin, breast cancer, anal cancer, endometrial cancer metastatic, and lung adenocarcinoma).

DISCUSSION

Data from Year 2 of the LITHE study confirmed that tocilizumab-MTX provided significantly greater inhibition of structural joint damage and significantly greater improvement in physical function than placebo-MTX. Treatment effects on signs and symptoms of RA were maintained (e.g., ACR 20/50/70 response) or showed improvement (e.g., SJC, TJC) during Year 2. When the placebo-MTX group was switched to open-label 8 mg/kg tocilizumab-MTX during Year 2, clinically significant improvements were observed in all measures assessed.

Rescue therapy steps included in the LITHE study design mimic treatment paradigms for patients with established RA, who often require changes in treatment to minimize disease activity[21,22,23]. However, these steps significantly complicate data analysis. For example, almost all patients initially assigned to placebo-MTX in Year 1 received 8 mg/kg tocilizumab-MTX during Year 2. As expected, many measures of efficacy, such as mean change from baseline in GmTSS, improved in this group during Year 2. Analyses of co-primary efficacy endpoints used imputation methods for missing data or censored data after switch to rescue therapy or withdrawal. To address potential bias introduced by imputation methods, sensitivity analyses that included postwithdrawal and rescue data were performed for both co-primary endpoints. Results of the sensitivity analyses confirmed the robustness of the primary analyses and showed that significant differences were retained between tocilizumab-MTX and placebo-MTX groups when post-withdrawal and rescue data were included.

Data from the LITHE study confirm that tocilizumab has a rapid onset of efficacy that begins during the first few weeks of treatment, increases through the midpoint of Year 2, and is maintained thereafter. The rapid onset of efficacy associated with tocilizumab-MTX is comparable to that reported for combination therapy with tumor necrosis factor inhibitors and MTX[19,20,24]. A potential limitation of the study stems from the manner in which data were handled for each analysis. For example, in the 8 mg/kg tocilizumab-MTX group, the proportion of patients who attained DAS28 < 2.6 (64.7%) and DAS28 ≤ 3.2 (76.3%) in Year 2 was higher than might have been expected compared with the proportion of patients who attained ACR20/50/70 response (54.5%, 38.9%, 22.4%, respectively). However, rescue data were excluded in DAS28 < 2.6 calculations, and patients who switched to rescue therapy or withdrew were classified as nonresponders in analyses of ACR response.

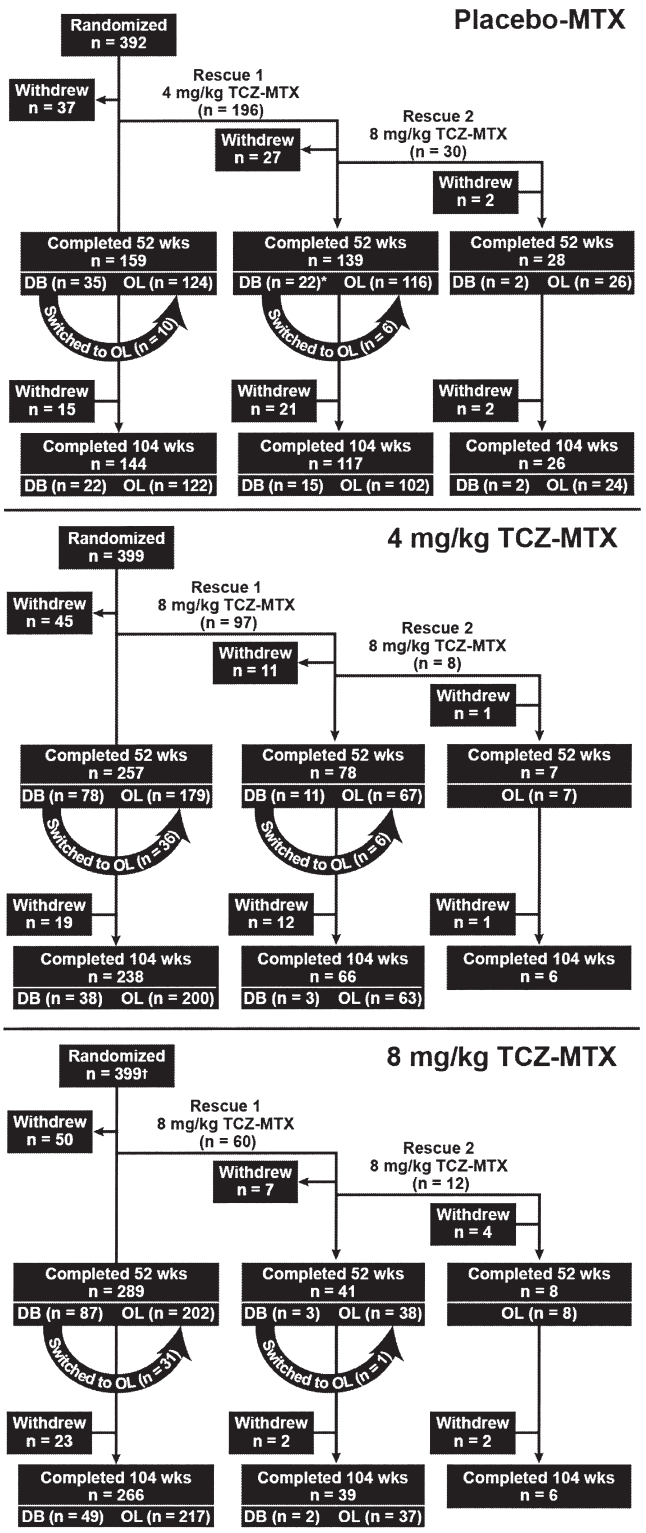
Additionally, IL-6 blockade has a profound effect on the acute-phase response[12], an important component of the DAS28-ESR formula. Therefore, comparisons between different measures of efficacy in our study must consider these caveats.

Given that most patients switched to open-label 8 mg/kg tocilizumab-MTX during Year 2 of the LITHE study, straightforward comparisons between the 4 mg/kg and 8 mg/kg tocilizumab-MTX groups are not possible. Data from Year 1 of the LITHE study demonstrate that 4 mg/kg tocilizumab-MTX is an effective dose; however, because of the study design, 4 mg/kg tocilizumab-MTX data were limited in Year 2; therefore, efficacy and safety analyses during Year 2 focus on 8 mg/kg tocilizumab-MTX. Overall, 8 mg/kg tocilizumab-MTX was associated with increasing efficacy, followed by a sustained effect [inhibition of progression of joint damage, clinical response (DAS28-ESR, LDAS)] over 2 years. Continuing clinical benefit was reflected in DAS28-ESR response rates because mean DAS28-ESR scores continued to decrease over 104 weeks. Patients initially randomized to 8 mg/kg tocilizumab-MTX, who received this dose for up to 2 years, showed the greatest benefit.

As observed during Year 1 of this study[11] and in other clinical trials[25], tocilizumab therapy was associated with increased risk for serious infections and elevations in hepatic enzyme and plasma lipid levels. Rates of serious infection were within the range observed in other populations of patients with RA, including those treated with tumor necrosis factor inhibitors (5.1–5.3/100 PY) and DMARD (4.1/100 PY)[26,27]. These AE are generally treatable and reversible and, in the current study, led to withdrawal in a minority of cases. For patients whose only dose of tocilizumab was 8 mg/kg, cumulative rates of premature withdrawal because of AE were 9.17/100 PY at Year 1 and 7.3/100 PY up to Week 104.

Safety data from patients who switched from 4 to 8 mg/kg tocilizumab-MTX must be interpreted with caution because 78 patients initially randomized to 4 mg/kg tocilizumab-MTX withdrew before dose escalation, primarily because of AE[28]. These patients were not included in the safety analysis of patients treated with 4 mg/kg tocilizumab-MTX who switched to 8 mg/kg tocilizumab-MTX but were included in the overall safety analysis of patients treated with 4 mg/kg tocilizumab-MTX[28]. In addition, criteria for dose escalation, dose continuation, or both were based on efficacy results that were predetermined per study protocol. Of note, the design of the LITHE study introduces a selection bias: patients who withdrew from the study while receiving 4 mg/kg tocilizumab-MTX do not contribute safety data to the analysis of the switching group but continue to contribute to the rates in the 4 mg/kg tocilizumab pooled analysis.

Overall, malignancy rates were low among the



APPENDIX 1. Patient disposition in Year 1 and Year 2 of LITHE. *One patient was excluded because double-blind 4 mg/kg tocilizumab-MTX rather than open-label 8 mg/kg tocilizumab-MTX was mistakenly administered at the end of Year 1. †For 1 patient, no record of treatment withdrawal or of Week 104 completion was available because the study site closed. DB: double-blind; MTX: methotrexate; OL: open-label; TCZ: tocilizumab.

tocilizumab- and placebo-treated groups and within the range observed in other populations of patients with RA, including those treated with abatacept (0.61/100 PY) and DMARD (0.67–1.77/100 PY)[29]. However, as observed during Year 1 of LITHE, malignancy rates during Year 2 remained greater in the 4 mg/kg tocilizumab-MTX group (1.92/100 PY) than in the placebo-MTX and 8 mg/kg tocilizumab-MTX groups (0.70 and 0.98/100 PY, respectively). Why the malignancy rate was higher in the 4 mg/kg tocilizumab-MTX group during Year 1 is unclear; however, the rate was unlikely to change appreciably during Year 2 because the number of PY increased only modestly. During Year 2, the number of PY increased 13% in the placebo-MTX group, 60% in the 4 mg/kg tocilizumab-MTX group, and 321% in the 8 mg/kg tocilizumab-MTX group; in the latter, the disproportionately large increase in PY was because most patients switched from placebo-MTX or 4 mg/kg tocilizumab-MTX to 8 mg/kg tocilizumab-MTX in Year 2. Increased malignancy rates were not observed in the 4 mg tocilizumab groups of other phase III trials[4,6].

Tocilizumab-MTX significantly inhibited the progression of structural joint damage and significantly improved physical function in patients with RA compared with placebo-MTX. The benefits of tocilizumab observed during Year 1 of the LITHE study were either maintained or further improved during Year 2. Tocilizumab positively affected all aspects of RA, including signs and symptoms. No new safety signals were noted in tocilizumab-treated patients for up to 104 weeks of treatment. The extension phase of the LITHE study (Years 3–5) is continuing and will provide additional longterm efficacy and safety data.

ACKNOWLEDGMENT

The authors thank Lynn Brown, PhD, and Maribeth Bogush, PhD, for assistance in writing this report.

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APPENDIX 2. Summary of change from baseline in the ACR core set measures at Week 104 (intent-to-treat population).

	SJC, 66 Joint Count	TJC, 68 Joint Count	Patient Global VAS, mm	Physician Global VAS, mm	Patient Pain VAS, mm	CRP, mg/dl	ESR, mm/h	HAQ-DI
Placebo-MTX, n = 393								
n	391	391	137	139	137	139	139	127
Mean	–3.5	–5.9	–33.2	–43.9	–25.6	–1.6346	–30.7	–0.50
SD	11.65	17.07	26.35	21.55	24.44	2.28001	22.26	0.612
Median	–2.0	–3.0	–33.0	–47.0	–28.0	–0.8890	–30.0	–0.50
Minimum-maximum	–58 to 43	–65 to 42	–89 to 29	–87 to 25	–78 to 45	–14.927 to 1.150	–108 to 30	–2.3 to 1.4
4 mg/kg tocilizumab-MTX, n = 399								
n	399	399	228	229	228	231	231	218
Mean	–9.0	–13.6	–31.6	–49.1	–26.6	–1.6863	–35.4	–0.58
SD	10.76	16.53	27.05	20.33	25.39	2.20965	25.07	0.608
Median	–8.0	–13.0	–32.0	–50.0	–26.0	–1.0820	–32.0	–0.50
Minimum-maximum	–57 to 21	–68 to 35	–100 to 60	–94 to 22	–100 to 36	–12.240 to 5.140	–117 to 55	–3.0 to 1.1
8 mg/kg tocilizumab-MTX, n = 398								
n	397	397	248	250	248	251	247	231
Mean	–11.3	–17.7	–33.9	–48.7	–28.9	–2.3068	–36.9	–0.61
SD	11.31	16.73	26.60	22.20	25.47	2.65256	23.39	0.661
Median	–10.0	–17.0	–32.5	–50.0	–27.0	–1.5400	–33.0	–0.50
Minimum-maximum	–62 to 48	–67 to 48	–95 to 39	–97 to 48	–96 to 34	–19.281 to 3.359	–114 to 57	–2.9 to 1.5

Last-observation-carried-forward was used for TJC and SJC; no imputation was used for missing HAQ score, CRP, ESR, and VAS assessments. All assessments were set to missing from the time a patient receives escape therapy, and only pre-escape therapy joint count assessments were carried forward. CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; HAQ-DI: Health Assessment Questionnaire Disability Index; SJC: swollen joint count; TJC: tender joint count; VAS: visual analog scale; ACR: American College of Rheumatology; MTX: methotrexate.

APPENDIX 3. Rate of serious adverse events (AE) ≥ 0.4 per 100 patient-years (PY) in any group (safety population). PY exposure refers to the duration in treatment phase, calculated from the date treatment phase started to the date of the next treatment phase or, if the last treatment phase, the date of last safety assessment plus 1. Multiple occurrences of the same AE in one individual are counted once. Values are listed in descending order of total PY (sum of values in parentheses) across all treatment groups. Categories with identical total PY values are listed in alphabetical order. MTX: methotrexate.

AE, n (per 100-PY)	Placebo-MTX (PY), n = 392	4 mg/kg Tocilizumab-MTX (PY), n = 597	8 mg/kg Tocilizumab-MTX (PY), n = 983
Pneumonia	2 (0.7)	3 (0.6)	5 (0.4)
Gastroenteritis	2 (0.7)	2 (0.4)	1 (0.1)
Abortion spontaneous	2 (0.7)	—	—
Cellulitis	—	1 (0.2)	6 (0.5)
Breast cancer	1 (0.4)	1 (0.2)	—
Cholelithiasis	1 (0.4)	—	3 (0.2)
Spinal compression fracture	1 (0.4)	—	3 (0.2)
Acute myocardial infarction	—	2 (0.4)	1 (0.1)
Anaphylactic reaction	—	2 (0.4)	1 (0.1)
Anemia	1 (0.4)	—	1 (0.1)
Basal cell carcinoma	—	2 (0.4)	1 (0.1)
Deep vein thrombosis	1 (0.4)	—	1 (0.1)
Intervertebral disc protrusion	1 (0.4)	—	1 (0.1)
Accident	1 (0.4)	—	—
Alcohol poisoning	1 (0.4)	—	—
Anaphylactic shock	—	2 (0.4)	—
Angioedema	1 (0.4)	—	—
Ankle fracture	1 (0.4)		
Bone marrow failure	1 (0.4)	—	—
Depression	1 (0.4)	—	—
Gastroenteritis viral	—	2 (0.4)	—
Genital hemorrhage	1 (0.4)	—	—
Hemoptysis	1 (0.4)	—	—
Herpes zoster	1 (0.4)	—	—
Hiatus hernia	1 (0.4)	—	—
Hypotension	1 (0.4)		
Jaw cyst	1 (0.4)	—	—
Large intestinal ulcer	1 (0.4)	—	—
Prostate cancer	—	2 (0.4)	—
Renal failure	1 (0.4)	—	—
Respiratory failure	1 (0.4)		
Transient ischemic attack	1 (0.4)	—	—
Urinary tract infection	1 (0.4)	—	—
Vasculitis	—	2 (0.4)	
Ventricular fibrillation	1 (0.4)	—	—
Wegener's granulomatosis	1 (0.4)	—	—

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APPENDIX 4. Summary of worst Common Toxicity Criteria grades in clinical laboratory test results by trial treatment. Data from patients who switched from tocilizumab 4 mg/kg-MTX to tocilizumab 8 mg/kg-MTX are not included. MTX: methotrexate.

	Placebo-MTX, n = 392	4 mg/kg Tocilizumab-MTX, n = 146	8 mg/kg Tocilizumab-MTX, n = 532
White blood cell			
N	390	146	532
Normal	364 (93.3)	111 (76.0)	340 (63.9)
Grade 1	22 (5.6)	20 (13.7)	113 (21.2)
Grade 2	2 (< 1)	12 (8.2)	75 (14.1)
Grade 3	—	2 (1.4)	4 (< 1)
Grade 4	2 (< 1)	1 (< 1)	—
Platelets			
N	390	146	532
Normal	383 (98.2)	133 (91.1)	447 (84.0)
Grade 1	6 (1.5)	10 (6.8)	79 (14.8)
Grade 2	—	2 (1.4)	4 (< 1)
Grade 3	—	—	1 (< 1)
Grade 4	1 (< 1)	1 (< 1)	1 (< 1)
Lymphocytes			
N	389	145	527
Normal	316 (81.2)	109 (75.2)	401 (76.1)
Grade 1	28 (7.2)	8 (5.5)	26 (4.9)
Grade 2	33 (8.5)	24 (16.6)	89 (16.9)
Grade 3	10 (2.6)	3 (2.1)	11 (2.1)
Grade 4	2 (< 1)	1 (< 1)	—
Neutrophils			
N	388	145	527
Normal	368 (94.8)	112 (77.2)	287 (54.5)
Grade 1	12 (3.1)	13 (9.0)	124 (23.5)
Grade 2	5 (1.3)	15 (10.3)	91 (17.3)
Grade 3	1 (< 1)	3 (2.1)	22 (4.2)
Grade 4	2 (< 1)	2 (1.4)	3 (< 1)
Aspartate aminotransferase			
N	390	146	532
Normal	302 (77.4)	75 (51.4)	202 (38.0)
Grade 1	84 (21.5)	58 (39.7)	299 (56.2)
Grade 2	4 (1.0)	10 (6.8)	29 (5.5)
Grade 3	—	3 (2.1)	2 (< 1)
Grade 4	—	—	—
Alanine aminotransferase			
N	390	146	532
Normal	265 (67.9)	57 (39.0)	131 (24.6)
Grade 1	108 (27.7)	66 (45.2)	293 (55.1)
Grade 2	15 (3.8)	14 (9.6)	92 (17.3)
Grade 3	2 (< 1)	9 (6.2)	16 (3.0)
Grade 4	—	—	—
Total bilirubin			
N	390	146	532
Normal	384 (98.5)	130 (89.0)	456 (85.7)
Grade 1	6 (1.5)	12 (8.2)	50 (9.4)
Grade 2	—	4 (2.7)	25 (4.7)
Grade 3	—	—	1 (< 1)
Grade 4	—	—	—

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