EXTENDED REPORT

Adding tocilizumab or switching to tocilizumab monotherapy in methotrexate inadequate responders: 24-week symptomatic and structural results of a 2-year randomised controlled strategy trial in rheumatoid arthritis (ACT-RAY)

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► Additional supplementary data are published online only. To view the files please visit the journal online http://dx.doi.org/10.1136/annrheumdis-2011-201282

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Accepted 7 March 2012

ABSTRACT

Objective In patients with active rheumatoid arthritis (RA) despite methotrexate, to compare the efficacy of adding tocilizumab to that of switching to tocilizumab monotherapy.

Methods Double-blind, 2-year study in which adults with active RA (DAS28 >4.4) despite methotrexate were randomly assigned either to continue methotrexate with the addition of tocilizumab (MTX+TCZ) 8 mg/kg every 4 weeks or switch to tocilizumab and placebo (TCZ+PBO). The primary endpoint was the DAS28–erythrocyte sedimentation rate (ESR) remission rate at week 24. Secondary objectives included other symptomatic outcomes, quality of life and progression of structural damage.

Results Of 556 randomly assigned patients, 512 (92%) completed 24 weeks. DAS28–ESR remission rates were 40.4% for TCZ+MTX and 34.8% for TCZ+PBO (p=0.19); American College of Rheumatology 20/50/70/90 rates were 71.5%/45.5%/24.5%/5.8% (TCZ+MTX) and 70.3%/40.2%/25.4%/5.1% (TCZ+PBO; differences not significant). A significant difference between groups was seen for low DAS28 (61.7% vs 51.4%). Radiographic progression was small and not different between groups (Genant–Sharp score progression ≤ smallest detectable change in 91% (TCZ+MTX) and 87% (TCZ+PBO)). Rates per 100 patient-years of serious adverse events and serious infections were 21 and six, respectively, for TCZ+MTX and 18 and six, respectively, for TCZ+PBO. Alanine aminotransferase elevations greater than threefold the upper limit of normal occurred in 7.8% and 1.2% of TCZ+MTX and TCZ+PBO patients, respectively.

Conclusion No clinically relevant superiority of the TCZ+MTX add-on strategy over the switch to tocilizumab monotherapy strategy was observed. The combination was more commonly associated with transaminase increases. Meaningful clinical and radiographic responses were achieved with both strategies, suggesting that tocilizumab monotherapy might be a valuable treatment strategy in suitable RA patients.

One of the major long-term objectives of rheumatoid arthritis (RA) treatment is to prevent functional impairment as a result of bone damage, tendon or ligament rupture and cartilage breakdown. Persistent inflammation at the level of the joint (synovitis and osteitis) or the whole body (reflected in acute phase reactants) is among the most important predictors of subsequent structural deterioration.[1] Inflammation is also responsible for symptoms such as pain, fatigue and disability that impair the patient's quality of life.[2] Structural deterioration can be evaluated over months using radiological scoring systems.[3] Therefore, the short-term objective of RA treatment is to improve the patient's condition by abrogating inflammation and by sustaining this, thereby achieving the longer term objective of stopping radiological progression.[1]

Methotrexate is considered the cornerstone of therapy to achieve this goal. When there is inadequate disease control with methotrexate alone, the current recommendation is to add a tumour necrosis factor blocker or another approved biological agent.[4] However, as evidenced by registries of routine clinical practice treatment, approximately one third of RA patients are being treated with biological monotherapy, that is without concomitant methotrexate.[5 6] There are many reasons for stopping methotrexate or initiating biological agents as a monotherapy. In daily practice, frequent methotrexate-induced gastrointestinal disorders (eg, nausea) have been reported as leading to poor patient compliance.[7] Moreover, the use of methotrexate may lead to other safety issues such as haematological and hepatic adverse events. Such limitations explain why it is important to evaluate a switch strategy to biological monotherapy in addition to traditional add-on strategies (ie, the addition of a biological agent to methotrexate).

Tocilizumab, a humanised antihuman interleukin-6 receptor monoclonal antibody[8] has proved its efficacy and safety in RA patients continuing to receive methotrexate[9 10] and as biological monotherapy.[11] The latter is supported by data from a head-to-head trial showing that tocilizumab was more efficacious than methotrexate in patients who had not failed previous treatment with methotrexate or biological agents.[12] Because methotrexate is the current recommended first-line therapy, the question arises as to whether tocilizumab should

be added to methotrexate (add-on strategy) or methotrexate could be stopped when commencing tocilizumab (switch strategy) in patients with inadequately controlled disease. The only data comparing the two strategies is from a phase II study with a small sample size and no structural outcome measures to indicate the superiority of the add-on strategy.[13]

We therefore conducted a 2-year trial with the objective of assessing the efficacy and safety profile of either adding tocilizumab to methotrexate or switching methotrexate to tocilizumab monotherapy in patients with persistent active disease despite methotrexate therapy. Here, we report the first 24-week clinical and radiological data.

PATIENTS AND METHODS

Study design

This report covers the planned analysis of the first 24 weeks (including the primary endpoint) of an on-going 2-year double-blind placebo controlled parallel-group clinical trial (NCT00810199, EudraCT no 2008-001847-20). The treatment allocation of individual patients remained blinded for patients, site personnel and the data analysis/interpretation team, except for the separate subgroup technically preparing the data.

The study was approved by the appropriate institutional review boards/ethics committees with written informed consent obtained from each patient before study participation. The study was conducted in full accordance with International Conference on Harmonisation/good clinical practice and the principles, laws and regulations of the countries in which the research was conducted.

Patients

Eligible patients had confirmed RA according to the 1987 American College of Rheumatology (ACR) criteria with active disease defined as disease activity score based on 28 joints–erythrocyte sedimentation rate (DAS28–ESR) greater than 4.4 at baseline and 4.0 or more at screening, and had been receiving methotrexate for at least 12 weeks, with a stable dose of at least 15 mg/week for 6 weeks or longer before starting study treatment. For inclusion, patients were also required to have bone damage with radiographic evidence of at least one joint with definite erosion attributable to RA as determined by a central reader. Major exclusion criteria included severe comorbidities, any previous use of biological agents as well as any conventional disease-modifying antirheumatic drug treatment other than methotrexate during the month (3 months for leflunomide) preceding the baseline visit (see supplementary data, available online only, for full inclusion and exclusion criteria).

Study treatment

Patients were randomly assigned either to the add-on or the switch strategy group (see supplementary data, available online only, for study design schematic). Randomisation was stratified by study site and baseline DAS28–ESR (≤ or >5.5) using a minimisation algorithm. All patients received open-label tocilizumab 8 mg/kg intravenously every 4 weeks. Treatment with methotrexate/placebo was double-blind: all patients received identical capsules of either placebo (switch strategy arm) or methotrexate 2.5 mg (add-on strategy arm), with the number of capsules at study entry being consistent with prestudy dosage. Tocilizumab and/or disease-modifying antirheumatic drug treatment was reduced or temporarily interrupted in patients with alanine aminotransferase or aspartate transaminase values greater than one to three times the upper limit of normal (ULN), and was discontinued for persistent increases greater than three times ULN.

Concomitant RA treatments

Oral corticosteroids (≤10 mg/day prednisone or equivalent) and non-steroidal anti-inflammatory drugs were permitted as long as doses had been stable for at least 25 of 28 days before the start of study treatment. Alterations in the non-steroidal anti-inflammatory drug dose were not recommended during the study, particularly during the first 24 weeks. The corticosteroid dose could not be changed during the first 24 weeks of the study.

Collected patient data and assessments

Data collected at baseline included demographics and disease characteristics such as RA disease duration. At baseline and every 4 weeks thereafter the following parameters were assessed: tender joint count, swollen joint count, health assessment questionnaire–disability index (HAQ–DI), patient's global assessment, physician's global assessment, C-reactive protein (CRP), ESR. Quality of life was assessed at baseline and at weeks 4, 8, 12 and 24 using the rheumatoid arthritis quality of life questionnaire (RAQoL). At each visit, patients were monitored for adverse events, vital signs and laboratory tests (eg, blood counts, transaminases, cholesterol). Radiographs of the hands/wrists and feet were obtained at baseline and week 24. Each radiograph was assessed applying the Genant-modified Sharp scoring system (GSS) by two independent readers (Perceptive Informatics Medical Imaging Services, Berlin, Germany) who were blinded to treatment assignment, chronological order of radiographs and patient's clinical status. The smallest detectable change (SDC) for GSS was computed based on the observed SD of difference between the x-ray readers,[14] whereas three readers in total participated in the campaign. The SDC is the smallest change that can be attributed to something more than observed variability of reader differences.

Statistical analysis

The clinical superiority of the tocilizumab plus methotrexate combination treatment in the phase II CHARISMA study[13] had an important influence on the statistical parts of the design.

To assess the working hypothesis that the add-on strategy (ie, initiation of tocilizumab plus continuation of methotrexate) would be superior to the switch strategy (ie, initiation of tocilizumab and discontinuation of methotrexate), the primary outcome measure of the study was defined as the percentage of patients in remission according to DAS28–ESR (DAS28 <2.6) at week 24. A two-sided statistical test of no difference between the two treatment arms at the 5% significance level was used. Specifically for the primary endpoint, as well as for similar endpoints, a logistic regression model was employed including the stratification factors used at randomisation (site and baseline DAS28 ≤ or >5.5) with a supportive Cochran–Mantel–Haenszel test stratified for the same parameters. Analysis of covariance models were used to compare continuous outcome measures.

Efficacy analyses were conducted in the intention-to-treat population (all randomly assigned and treated patients analysed in the arm they were randomly assigned to) with non-responder imputation for categorical variables (eg, DAS28 remission, ACR response), last observation carried forward until patient withdrawal for missing joint counts and no additional imputation of missing values.

The target sample size (235 patients per arm) was computed to provide 80% power to detect a 12.5% treatment effect

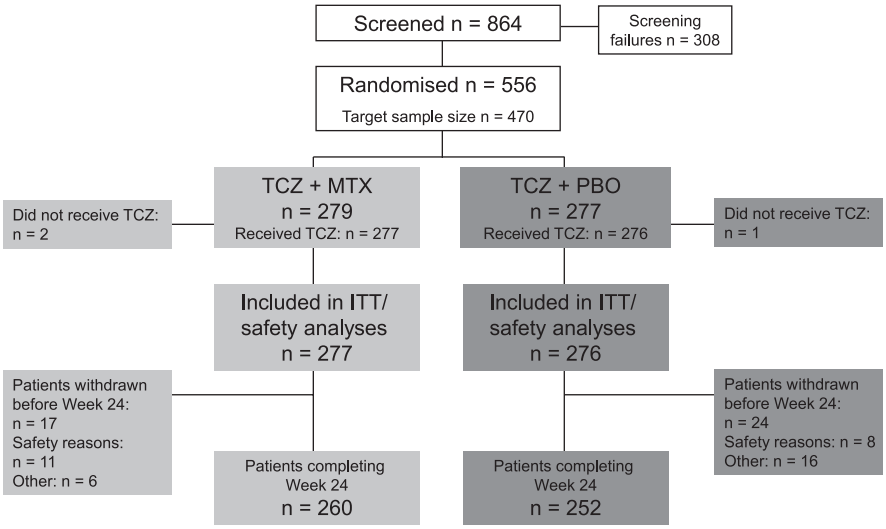

Figure 1 Patient disposition and study flow chart. ITT, intention-to-treat; MTX, methotrexate; PBO, placebo; TCZ, tocilizumab.

difference between an expected 42.5% DAS28 remission rate at week 24 in the add-on strategy arm versus 30% in the switch strategy arm.[12] This difference (12.5%) was deemed to be clinically relevant by the study's steering committee (see supplementary data, available online only).

The following additional endpoints were analysed in accordance with the European League Against Rheumatism (EULAR)/ACR collaborative recommendations for reporting RA disease activity in clinical trials:[11]

(1) Other outcome measures at week 24 included mean changes in DAS28–ESR and in selected variables (eg, swollen joint count, tender joint count, ESR, CRP, HAQ–DI, RAQoL); percentage of patients who improved during the 24 weeks of the study according to ACR20/50/70/90, EULAR response and the percentage of patients with DAS28 <3.2 (low disease activity state). Remission as defined by the 2010 ACR–EULAR criteria (Boolean definition),[15] simplified disease activity index ≤3.3 and clinical disease activity index ≤2.8 were analysed post hoc.
(2) To approach the concepts of onset of action and sustainability, changes over time of selected variables such as joint counts, CRP, pain and HAQ–DI were evaluated.
(3) The domain fatigue was evaluated using question 21 of the RAQoL questionnaire.
(4) Radiographic endpoints included changes from baseline in total GSS, erosion and joint space narrowing scores and the proportion of patients with no radiographic progression (progression defined as change in GSS >SDC or >0).

Safety endpoints included the incidence of adverse events (AE), serious AE, serious infections and specific laboratory abnormalities, which were analysed in the safety population (all treated patients with at least one post-dose assessment of safety, analysed according to the treatment received).

RESULTS

Patient flow and baseline characteristics

Figure 1 summarises the flow of patients. The predominant reason for screening failure (n=308) was the absence of radiological erosions (40% of screening failures). Five hundred and fifty-six patients were recruited, exceeding the target of 470 patients. This larger sample size increased the precision of the estimates.

Table 1 Baseline characteristics

	TCZ+MTX (N=277)	TCZ+PBO (N=276)
Women, n (%)	227 (81.9)	217 (78.6)
Age (years), mean (SD)	53.0 (13.4)	53.6 (11.9)
Patients aged ≥65 years, n (%)	53 (19.1)	52 (18.8)
BMI, kg/m², mean (SD)	26.3 (5.20)	26.5 (5.14)
Duration of RA, years, mean (SD)	8.2 (8.0)	8.3 (8.4)
Categorical duration of RA in years, n (%):		
<2	51 (18.4)	66 (23.9)
≥2 to <5	76 (27.4)	68 (24.6)
≥6 to <10	66 (23.8)	63 (22.8)
≥10	84 (30.3)	79 (28.6)
Swollen joint count, mean (SD)	14.4 (8.9)	15.3 (10.2)
Tender joint count, mean (SD)	25.8 (13.9)	26.6 (15.2)
DAS28–ESR, mean (SD)	6.33 (0.98)	6.36 (1.00)
HAQ–DI, mean (SD)	1.46 (0.66)	1.48 (0.60)
HAQ–DI <0.5, n (%)	17 (6.2)	14 (5.2)
Genant-modified Sharp score, mean (SD)	30.4 (31.8)	37.1 (40.5)
Methotrexate dose, mg/week, mean (SD)	16.0 (4.4)	16.2 (4.1)
Methotrexate dose, mg/week, median	15.0	15.0
No of previous DMARD (including methotrexate before study entry), mean (SD)	1.9 (1.1)	1.9 (1.0)
Oral steroid use, n (%)	136 (49.1)	135 (48.9)
Folic acid use, n (%)	215 (77.6)	224 (81.2)

BMI, body mass index; DMARD, disease-modifying antirheumatic drug; DAS28–ESR, disease activity score based on 28 joints–erythrocyte sedimentation rate; HAQ–DI, health assessment questionnaire–disability index; MTX, methotrexate; PBO, placebo; RA, rheumatoid arthritis; TCZ, tocilizumab.

Of the 556 randomly assigned patients, 512 (92%) completed the first 24 weeks of the trial. There were no clinically significant differences between the groups in the baseline characteristics except for a potentially relevant difference in GSS (table 1).

Clinical efficacy

The main efficacy results at week 24 are summarised in figure 2 and table 2 (also see supplementary data, available online only). Patients received mean weekly doses of methotrexate/placebo ranging from 15.2 to 15.9 mg/week and 15.8 to 16.3 mg/week

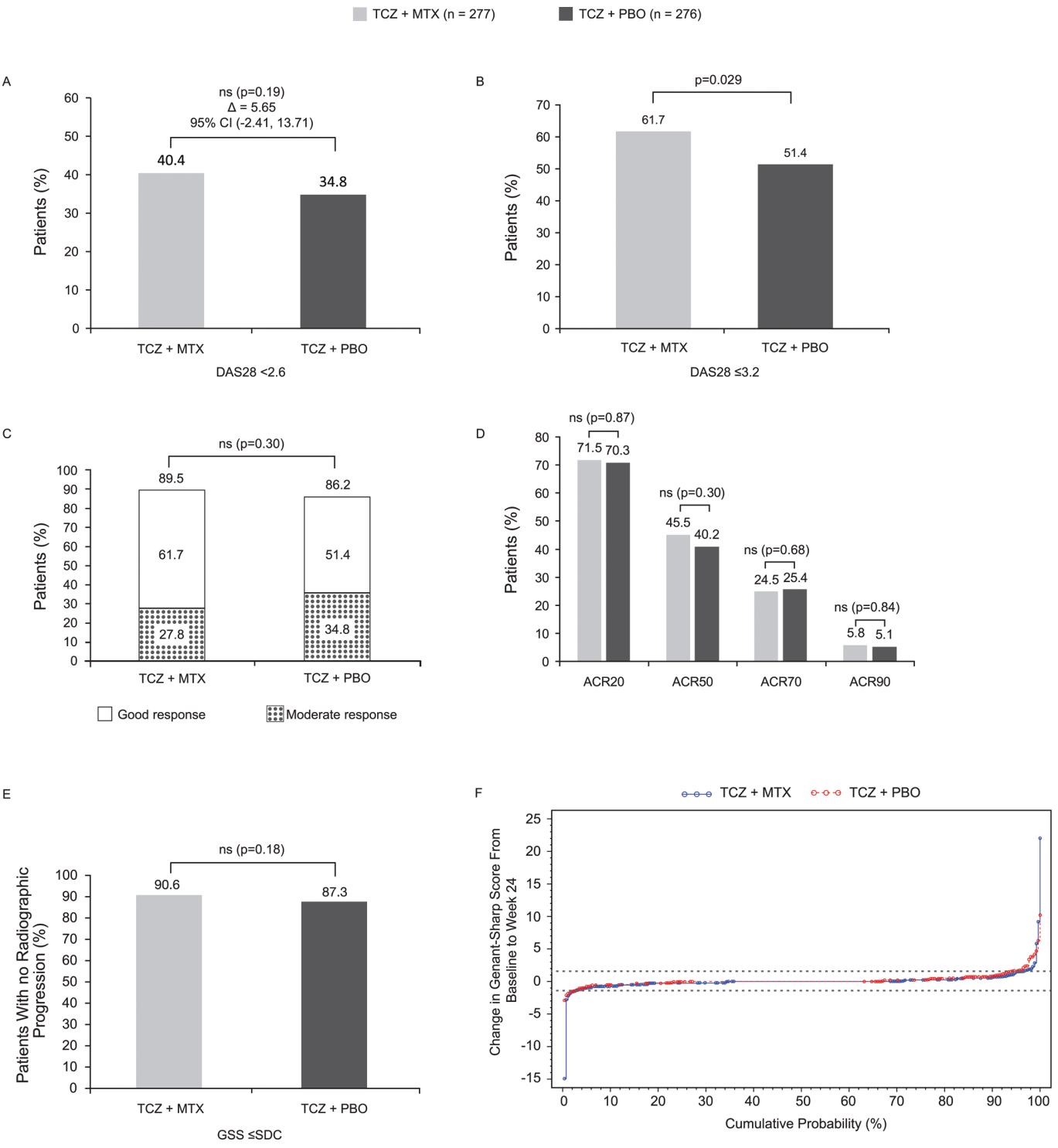

Figure 2 Binary composite indices and radiographic results at week 24 (intent-to-treat population). (A) Patients achieving remission (DAS28 <2.6), (B) low disease activity (DAS28 ≤3.2), (C) good or moderate European League Against Rheumatism responses, (D) ACR responses, (E) patients (%) with no radiographic progression in total GSS, and (F) cumulative distribution of change from baseline in total GSS. Dashed lines indicate smallest detectable change with data falling between these lines representing no change. ACR, American College of Rheumatology; DAS28, disease activity score based on 28 joints; GSS, Genant-modified Sharp Score; MTX, methotrexate; NS, not significant; PBO, placebo; TCZ, tocilizumab.

for the tocilizumab plus methotrexate and tocilizumab plus placebo groups, respectively. Both treatment strategies showed a highly relevant clinical treatment effect. The study did not demonstrate a statistically significant difference between the two groups in DAS28–ESR remission rates (primary endpoint). The actual absolute difference between groups (5.65%, 95% CI −2.41% to 13.71%, p=0.19) was much smaller than what had been considered clinically relevant a priori (12.5%). For other endpoints, the differences between the treatment groups at week 24 were mostly not statistically significant and/or small, but with a numerical trend towards superiority of the add-on strategy. The difference between groups in the proportion of

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Table 2 Efficacy results at week 24

Variable	TCZ+MTX (N=277)	TCZ+PBO (N=276)	p Value (between group)
DAS28 remission rate, %	40.4	34.8	0.19
Change in DAS28, mean (SD)	−3.43 (1.33)	−3.21 (1.31)	0.051
LDAS, %	61.7	51.4	0.029
EULAR good plus moderate responders, %	89.5	86.2	0.30
ACR–EULAR Boolean remission rate, %	6.9	5.4	0.53
SDAI remission rate (≤3.3), %	11.9	9.8	0.56
CDAI remission rate (≤2.8), %	11.9	7.6	0.12
Change in tender joint count, mean (SD)	−17.25 (13.35)	−17.00 (13.64)	0.52
Change in swollen joint count, mean (SD)	−11.33 (8.04)	−11.75 (9.45)	0.61
Change in patient's global assessment of disease activity, mean (SD)	−34.3 (25.68)	−32.4 (24.34)	0.20
Change in physician's global assessment of disease activity, mean (SD)	−40.7 (19.55)	−38.5 (21.65)	0.084
Change in patient's global assessment of pain, mean (SD)	−29.3 (26.64)	−29.8 (24.92)	0.30
Change in RAQoL, mean (SD)	−5.97 (7.95)	−5.19 (7.06)	0.31*
Change in total GSS, mean (SD)	0.08 (1.88)	0.22 (1.11)	0.26
Change in JSN score, mean (SD)	0.08 (1.48)	0.11 (0.70)	0.76
Change in erosion score, mean (SD)	−0.01 (0.78)	0.11 (0.63)	0.066
Patients with no progression in GSS (≤SDC), %	90.6	87.3	0.18
Patients with no progression in GSS (≤0), %	65.7	59.1	0.088

ACR, American College of Rheumatology; CDAI, clinical disease activity index; DMARD, disease-modifying antirheumatic drug; DAS28, disease activity score based on 28 joints; EULAR, European League Against Rheumatism; GSS, Genant-modified Sharp score; JSN, joint space narrowing; LDAS, low disease activity score; MTX, methotrexate; PBO, placebo; RAQoL, rheumatoid arthritis quality of life questionnaire; SDAI, simplified disease activity index; SDC, smallest detectable change; TCZ, tocilizumab. *p Value from a 2-sided Wilcoxon rank-sum test of no difference between the two treatment arms.

patients achieving low disease activity (DAS28–ESR <3.2) was 10.3% (p=0.029).

Fatigue, as assessed by the proportion of patients answering 'yes' to question 21 of the RAQoL questionnaire ('I feel tired whatever I do') affected 75.6% and 73.3% of patients at baseline (add-on vs switch, respectively, p=0.79) and 51.9% and 50.0% at week 24 (p=0.68). Clinical parameters and CRP improved rapidly in both groups (figure 3A–D). For all these variables a sustained or continuously increasing effect size was observed in both treatment groups through the first 24 weeks of the study.

Progression of structural damage

There were no statistically significant intergroup differences in any of the evaluated continuous outcome measures (table 2, figure 3E). The SDC from baseline in GSS was 1.5, indicating a high agreement of the readings, therefore allowing for the detection of changes from baseline less than −1.5 and greater than 1.5. Radiographic progression was defined in two ways: any change in GSS greater than zero or greater than SDC. Based on the second definition the proportion of patients with no radiographic progression was 87.3% and 90.6% (GSS ≤SDC) in the tocilizumab plus placebo and tocilizumab plus methotrexate groups, respectively, and was generally very low in those patients who still had progressive structural damage. The changes from baseline in total GSS at week 24 were distributed similarly in the two groups (figure 2F).

Safety

A safety overview is presented in table 3. Overall rates per 100 patient-years of AE and serious AE were similar between groups. A total of 17 patients (6.1%) in the tocilizumab plus methotrexate group and 16 patients (5.8%) in the tocilizumab plus placebo group experienced serious AE, the most common of which were infections (seven events in each group) and cardiac disorders (three and four events in the two groups, respectively). There was a total of three deaths in the first 24 weeks and a fourth patient died from an AE that started within the first 24 weeks (two each in either group). The causes of death in these four patients were: sepsis; septic shock preceded by scrotal abscess, skin necrosis, acute renal failure and congestive heart failure; myocardial infarction; and sepsis with meningitis. AE-related discontinuations and dose modifications occurred in 3.6% and 27.4% of tocilizumab plus methotrexate patients and 2.5% and 18.5% of tocilizumab plus placebo patients, respectively.

Alanine aminotransferase elevations from normal at baseline to greater than ULN and to more than three times ULN at one or more time points during 24 weeks occurred in 48.8% and 7.8% of tocilizumab plus methotrexate and in 27.6% and 1.2% of tocilizumab plus placebo patients, respectively. For aspartate transaminase, such elevations occurred in 34.2% and 1.9% (tocilizumab plus methotrexate) and in 19.2% and 0.4% (tocilizumab plus placebo) of patients, respectively, indicating a trend towards lower rates of liver enzyme elevations with tocilizumab monotherapy. As seen in previous studies with tocilizumab and also with other anti-inflammatory treatments, mean total cholesterol levels increased from 93.1 and 92.7 mg/dl at baseline to 102.4 and 103.5 mg/dl at week 24 in the tocilizumab plus methotrexate and tocilizumab plus placebo groups, respectively.

DISCUSSION

This study evaluated two different tocilizumab-based treatment strategies in patients with active RA and suggests that a clinically relevant effect with arrest of structural progression is observed at 24 weeks with both treatment strategies in the majority of patients. The study did not succeed at demonstrating that add-on strategy efficacy (combination therapy of tocilizumab plus methotrexate) was superior to the switch strategy (monotherapy tocilizumab plus placebo), although there were numerically small and not clinically meaningful differences in the primary and some secondary efficacy endpoints in favour of combination therapy. No differences were observed in safety, the exception being that the add-on strategy resulted in a numerically higher percentage of patients who had transaminase level increases compared with the switch strategy.

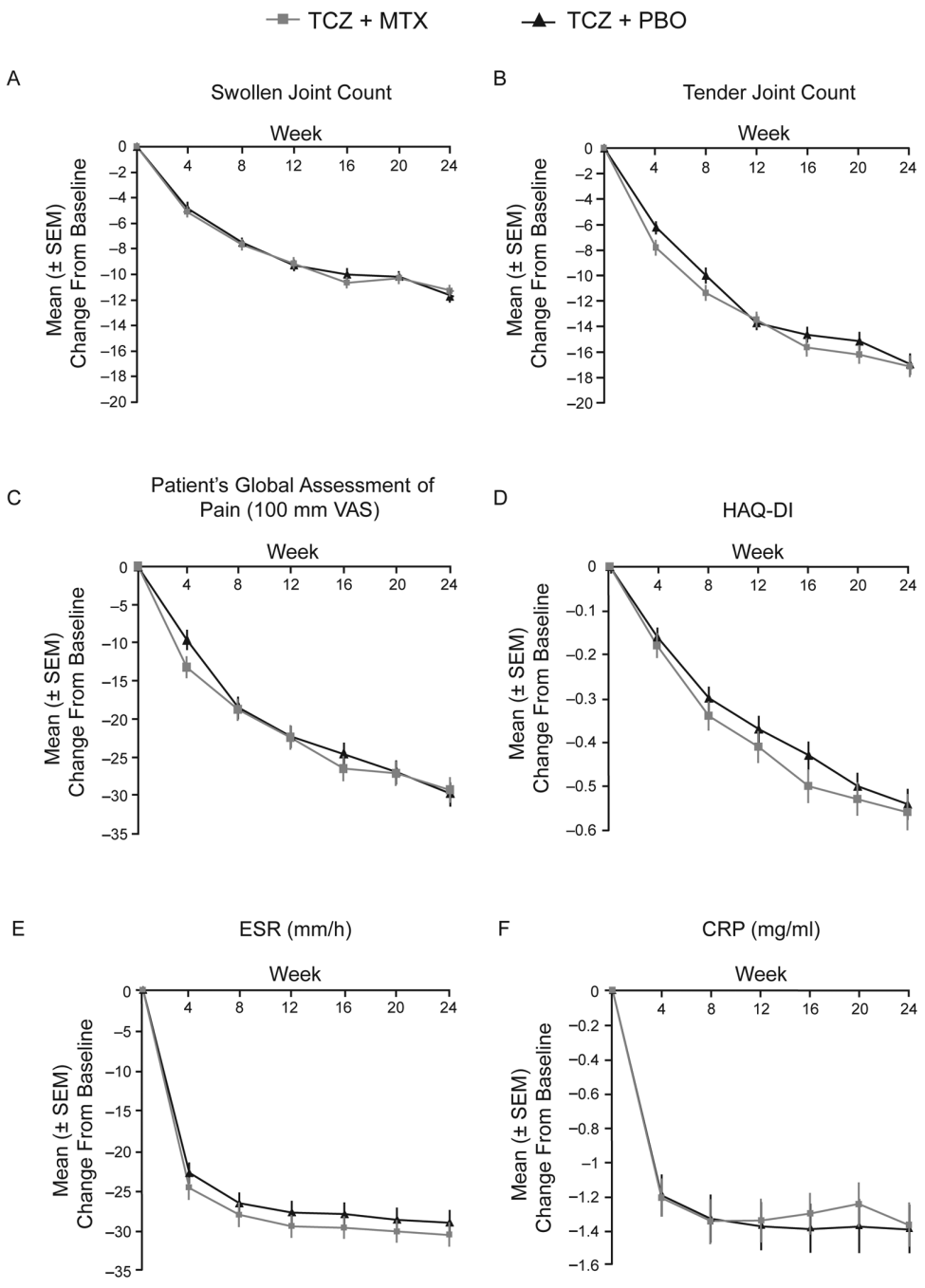

Figure 3 Changes from baseline in selected American College of Rheumatology core set variables over time (intent-to-treat population). (A) Mean change from baseline for swollen joint counts, (B) tender joint counts, (C) patient's global assessment of pain, (D) HAQ–DI, (E) ESR and (F) CRP. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HAQ–DI, health assessment questionnaire–disability index; MTX methotrexate; TCZ, tocilizumab; VAS, visual analogue scale.

This is the first study comparing the efficacy and safety of tocilizumab in combination with methotrexate and as monotherapy in inadequate responders to methotrexate with a sufficient sample size to address this question prospectively. The primary outcome measure (DAS28–ESR remission rate at 24 weeks) did not differ significantly between the two strategies. With the exception of the proportion of patients with low disease activity (DAS28–ESR <3.2) at 24 weeks, the secondary efficacy analyses supported the primary endpoint by not showing a between-group statistically significant difference. This interpretation is also supported by the changes over time in individual parameters (figure 2). Looking at the overall picture across different endpoints and time points there was a trend towards slightly higher responses with the add-on strategy (eg, 5.6% difference in DAS28 remission and 3.3% difference in patients with no radiological progression greater than SDC). Looking at the effect sizes and the fact that most of the differences are not statistically significant the trend in favour of the add-on strategy is considered clinically not meaningful.

As the study did not succeed at demonstrating the superiority of the add-on versus the switch strategy, we discuss here factors that could potentially have biased the study outcome, before

Table 3 Overview of adverse events, deaths, and liver enzyme elevations* until week 24

	TCZ+MTX	TCZ+PBO
	N=277	N=276
Total tocilizumab exposure (PY)	118.31	116.40
AE		
Total patients with ≥1 AE, % (n)	70.0% (194)	72.5% (200)
Total no of AE	581	544
Rate of AE (per 100 PY)	491	467
Serious AE		
Total patients with ≥1 serious AE, % (n)	6.1% (17)	5.8% (16)
Total no of serious AE	25	21
Rate of serious AE (per 100 PY)	21	18
Serious infections		
Total patients with ≥1 serious infections, % (n)	2.2% (6)	2.2% (6)
Total no of serious infections	7	7
Rate of serious infections (per 100 PY)	6	6
Total no of deaths	1†	2
ALT elevations, % (n‡)	N§=244	N§=243
>ULN–1.5 × ULN	25.8% (63)	16.5% (40)
>1.5–3 × ULN	15.2% (37)	9.9% (24)
>3–5 × ULN	5.7% (14)	0.8% (2)
>5 × ULN	2.0% (5)	0.4% (1)
AST elevations, % (n‡)	N§=257	N§=250
>ULN–1.5 × ULN	21.8% (56)	14.8% (37)
>1.5–3 × ULN	10.5% (27)	4.0% (10)
>3–5 × ULN	1.9% (5)	0.4% (1)
>5 × ULN	0.0% (0)	0.0% (0)

*Cumulative incidences weeks 1–24, excluding patients with elevations at baseline. Data including non-fasting samples.
†An additional patient in this group had an adverse event leading to death but died only after the 24-week cut-off.
‡Number of patient with a normal baseline and the highest value in the first 24 weeks within the indicated range. ULN=55 U/l for ALT and 40 U/l for AST.
§Number of patients with normal value at baseline.
AE, adverse event; ALT, alanine aminotransferase (glutamate pyruvate transaminase); AST, aspartate aminotransferase (glutamate oxaloacetate transaminase); MTX, methotrexate; PBO, placebo; PY, patient years; TCZ, tocilizumab; ULN, upper limit of normal.

rejecting the clinical study hypothesis. The study was powered to detect a 12.5% difference in DAS28–ESR remission rates at week 24 between the two arms, which is the minimum difference that the scientific steering committee considered to be clinically meaningful. This choice was supported by CHARISMA, a phase II dose-finding study, which indicated that combination therapy of tocilizumab with methotrexate might be superior to monotherapy (eg, DAS28 remission at week 16 achieved by 34% of combination therapy and 17% of monotherapy patients).[13] Based on the number of patients actually randomly assigned and the observed remission rate in the tocilizumab plus placebo arm the study was factually able to detect a difference of approximately 11% between the two strategies and as such had adequate discriminative power for a relevant treatment difference. The patients were selected based on the established definition of RA and their baseline characteristics were in concordance with earlier studies with tocilizumab or other biological agents, and were well balanced between the treatment arms. The only notable exception was baseline GSS, which showed more advanced structural damage in the switch group.

The doses of both methotrexate/placebo and tocilizumab were in line with approved labels. Furthermore, the methotrexate/placebo doses were similar between trial arms (table 1) and consistent with previous clinical trials evaluating combination methotrexate plus biological agent treatment[16–20] as well as with commonly prescribed methotrexate doses in clinical practice.[21–23] However, methotrexate/placebo doses were lower than in some current recommendations for the optimisation of methotrexate.[24 25]

In the absence of any methodological bias that could have artificially reduced the difference in efficacy between the two arms, we conclude that the answer to the question asked in the study 'Is the add-on strategy superior to the switch to monotherapy strategy?' is 'no' so that one could suggest that both strategies provide a similar benefit in terms of clinical and structural outcomes.

Safety outcomes were similar in the two arms, except for a numerically higher rate of increased transaminase levels with the add-on strategy. Overall, the incidence of events such as serious AE, serious infections and discontinuations was similar between the add-on and switch strategies, consistent with previous tocilizumab studies.

The data observed in this study suggest that tocilizumab monotherapy may be a valuable treatment strategy for certain RA patients requiring biological agents. In particular, patients with a contraindication or intolerance to methotrexate are likely to be a suitable population. Further confirmation of these data is required, including through the longer term observation of the patients recruited for this study as well as additional studies in other patient sets including the evaluation in daily practice via registries.

Contributors MD, KK, PPT, PGC, EMM, GS, CB and TWJH designed the study and analysed and interpreted the data. MD, TS, PPT, PGC, EMM, GS, HA, FNS, AH and TWJH along with other investigators were involved in generating the data at their clinical research sites. All authors were involved in writing the manuscript and approved it.

Funding The ACT-RAY study was funded by F Hoffmann-La Roche Ltd, Basel, Switzerland (Roche). Roche was involved in developing the study design, in the analysis and interpretation of the data, in the writing of the report, and in the decision to submit the paper for publication, through Roche employees, contractors and funding of third party support such as contract research organisations. All these activities happened in close collaboration with the external members of the scientific steering committee.

Competing interests MD has participated in symposia and advisory boards organised by Roche and received consulting fees and his department has received research grants from Roche for conducting clinical trials and/or clinical epidemiological studies. KK is an employee of F Hoffmann-La Roche. TS received consulting fees and research grants from Roche. PPT's department has received Roche funds as grants and consulting fees or honorarium. PPT is an employee of and has stock/stock options for GlaxoSmithKline. PGC has received research grants from Centocor Inc and Roche and has been a speaker for Astra Zeneca, Bioberica, Bristol-Myers Squibb, Centocor Inc, Merck Pharmaceuticals, Novartis Pharmaceutical Corporation, Pfizer and Roche. EMM has received consulting fees and been an educational lecturer for Abbott Immunology, Roche MSD, Pfizer and UCB. GS received consulting fees from Roche. FNS has consulted for Pfizer, UCB, Abbott and Roche and has been a speaker for Roche, Pfizer, Abbott and MSD, and his department has received research grants from Roche, Pfizer and Abbott. AH has no competing interests to report. CB is a contractor of F Hoffmann-La Roche. TWJH has received consulting fees and has been a speaker for Abbott Immunology, Axis Shield Diagnostics, Biotest AG, Bristol-Myers Squibb, Crescendo Bioscience, Roche, Novartis Pharmaceuticals, Schering-Plough, UCB and Wyeth-Pfizer.

Ethics approval The study was approved by the appropriate institutional review boards/ethics committees.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

Correction notice This article has been corrected since it was published Online First. The link to the supplementary data has been corrected.

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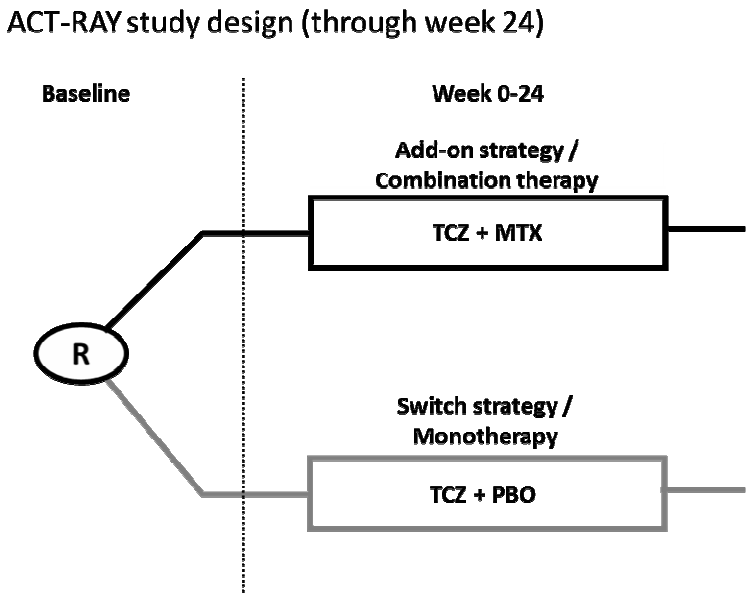
Study Design



Inclusion Criteria

To be eligible for this trial, patients must meet all of the following criteria:

1. Male or non-pregnant, non-nursing female
2. ≥ 18 years of age
3. Body weight ≤ 150 kg
4. Patients currently experiencing active moderate to severe RA (DAS28 > 4.4) according to the revised 1987 ACR criteria for the diagnosis of RA at baseline. At screening the DAS28 must be equal or greater than 4.0 (DAS28 ³ 4.0).
5. Radiographic evidence of at least one joint with definite erosion attributable to RA as determined by the central reading site. Any joint of the hands, feet or wrists can be considered with the exception of distal interphalangeal joints of the hands
6. Patients currently receiving MTX (oral or parenteral) for at least 12 weeks and who have received MTX at a stable dose of at least 15 mg/week for at least 6 weeks prior to treatment (day 1), with the following exception: 10 mg instead of 15 mg is acceptable in patients with a body weight < 50 kg, low grade toxicity to MTX (such as nausea), or calculated glomerular filtration rate (or creatinine clearance) < 60 mL/min. Patients with a history of parenteral (subcutaneous or intramuscular) MTX prior to baseline are eligible. However, prior to treatment (day 1) these patients must have been on a stable dose of oral MTX of at least 15 mg/week for at least 6 weeks.

7. If patients are receiving an oral corticosteroid, the dose must have been ≤ 10 mg/day prednisone (or equivalent) and stable for at least 25 out of 28 days prior to treatment (day 1)
8. Patients receiving treatment on an outpatient basis
9. Patients able and willing to give written informed consent and comply with the requirements of the study protocol

Exclusion Criteria

Patients with any of the following criteria will not be eligible to participate in the study:

Disease

1. Major surgery (including joint surgery) within 8 weeks prior to screening or planned major surgery within 6 months following randomization
2. Rheumatic autoimmune disease other than RA, including systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD), scleroderma, polymyositis, or significant systemic involvement secondary to RA (e.g. vasculitis, pulmonary fibrosis or Felty's syndrome). Patients with interstitial pulmonary fibrosis and still able to tolerate MTX therapy are permitted. Sjögren's Syndrome with RA is permitted
3. Functional class IV as defined by the ACR Classification of Functional Status in RA (largely or wholly incapacitated with patient bedridden or confined to wheelchair, permitting little or no self-care)
4. Prior history of or current inflammatory joint disease other than RA (e.g. gout, reactive arthritis, psoriatic arthritis, seronegative spondyloarthropathy, Lyme disease)

Drug-specific

5. Treatment with traditional DMARDs other than MTX within 1 month (for leflunomide 3 months) prior to baseline
6. Treatment with any investigational agent within 4 weeks (or 5 half-lives of investigational agent, whichever is longer) before screening
7. Previous treatment with TCZ.
8. Previous treatment with any biologic drug that is used in the treatment of RA
9. Any previous treatment with alkylating agents, such as cyclophosphamide or chlorambucil, or with total lymphoid irradiation
10. Treatment with IV gamma globulin, plasmapheresis or Prosorba® column within 6 months before baseline
11. Intraarticular or parenteral corticosteroids within 6 weeks prior to baseline

12. Immunization with a live/attenuated vaccine within 4 weeks prior to baseline

Laboratory analyses (at screening)

13. Serum creatinine > 142 µmol/L (1.6 mg/dL) in female patients and > 168 µmol/L (1.9 mg/dL) in male patients and no active renal disease
14. ALT (SGPT) or AST (SGOT) > 1.5 x ULN
15. Platelet count < 100 x 10^9/L (100,000/mm^3)
16. Hemoglobin < 85 g/L (8.5 g/dL; 5.3 mmol/L)
17. WBC count < 1.0 x 10^9/L (1000/mm3), absolute neutrophil count < 1.0 x 10^9/L (1000/mm^3). Patients enrolled prior to amendment based on a lower ANC threshold may continue to stay in the study, if deemed appropriate by the investigator.
18. Absolute lymphocyte count < 0.5 x 10^9/L (500/mm^3)
19. Positive HBsAg or HCV antibody
20. Total bilirubin > ULN
21. Triglycerides > 10 mmol/L (> 900 mg/dL) at screening (non-fasting or fasting)

General medical

22. Pregnant women or nursing (breastfeeding) mothers
23. Females of child-bearing potential who are not using reliable means of contraception (such as physical barrier [patient and partner], contraceptive pill or patch, spermicide and barrier, or intrauterine device)
24. History of severe allergic or anaphylactic reactions to human, humanized, or murine monoclonal antibodies
25. CXR evidence of any clinically significant abnormality
26. Evidence of serious uncontrolled concomitant cardiovascular, nervous system, pulmonary (including obstructive pulmonary disease), renal, hepatic, endocrine (including uncontrolled diabetes mellitus) or GI disease
27. In patients with a history of diverticulitis or diverticulosis requiring antibiotic treatment, the treating physician needs to consider the benefit-risk ratio
28. A history of chronic ulcerative lower GI disease such as Crohn's disease, ulcerative colitis, or other symptomatic lower GI conditions that might predispose to perforations
29. Uncontrolled disease states, such as asthma, psoriasis, or inflammatory bowel disease, where flares are commonly treated with oral or parenteral corticosteroids

30. Current liver disease as determined by investigator. Patients with prior history of ALT (SGPT) elevation are not excluded

31. Known active current or history of recurrent bacterial, viral, fungal, mycobacterial, or other infections (including but not limited to tuberculosis (TB) and atypical mycobacterial disease, clinically significant abnormalities on CXR as determined by the investigator, hepatitis B and C, and herpes zoster, but excluding fungal infections of nail beds), or any major episode of infection requiring hospitalization or treatment with IV antibiotics within 4 weeks of screening or oral antibiotics within 2 weeks prior to screening (does not apply to the treatment of latent TB)

32. History of, or currently active, primary or secondary immunodeficiency

33. Evidence of active malignant disease, malignancies active or diagnosed within the previous 5 years (including hematological malignancies and solid tumors, except nonmelanoma skin cancer that has been excised and cured)

34. Active TB requiring treatment within the previous 3 years. Patients treated for tuberculosis with no recurrence in 3 years are permitted.
    Latent TB: Patients with latent tuberculosis are not eligible, unless having started treatment with standard antimycobacterial therapy before initiating TCZ and have a negative CXR for active TB at screening. Therefore patients should be screened for latent TB, prior to biologics use, as per local guidelines or clinical practice in the country of study conduct. The assessment of the presence or absence of latent TB will take place during the screening period. However, if local practice or guidelines allow to refer to test results that were obtained prior to the screening period as part of routine clinical practice, this is allowed.

35. HIV positive patient

36. History of alcohol, drug, or chemical abuse within the 6 months prior to screening

37. Neuropathies or other painful conditions that might interfere with pain evaluation

38. Patients with lack of peripheral venous access

Supplemental Methods:

The study Steering Committee made assumptions concerning the expected DAS28-ESR remission rates at week 24 using the phase II dose-finding study CHARISMA as a guide. With a relatively small sample size CHARISMA indicated that TCZ + MTX combination therapy might be superior to TCZ monotherapy at week 16 (DAS28 remission achieved by 34% of combination therapy and 17% of monotherapy patients). The assumption of a 12.5% difference in the ACT-RAY study at week 24 (determined from an anticipated 42.5% remission rate in TCZ + MTX patients and a 30% remission rate in TCZ + PBO) was developed by the Steering Committee through discussions taking design differences as well as preliminary data from studies in slightly different populations into account. The steering committee considered the demonstration of a significant difference between the two treatment strategies with an estimated difference of 12.5% as valuable information for clinical practice, but also noted that different clinicians might find other differences clinically meaningful. The steering committee included, Maxime Dougados, Tom Huizinga, Paul Peter Tak (initially), Georg Schett, Emilio Martin Mola, and Philip Conaghan.

Supplemental Figure:

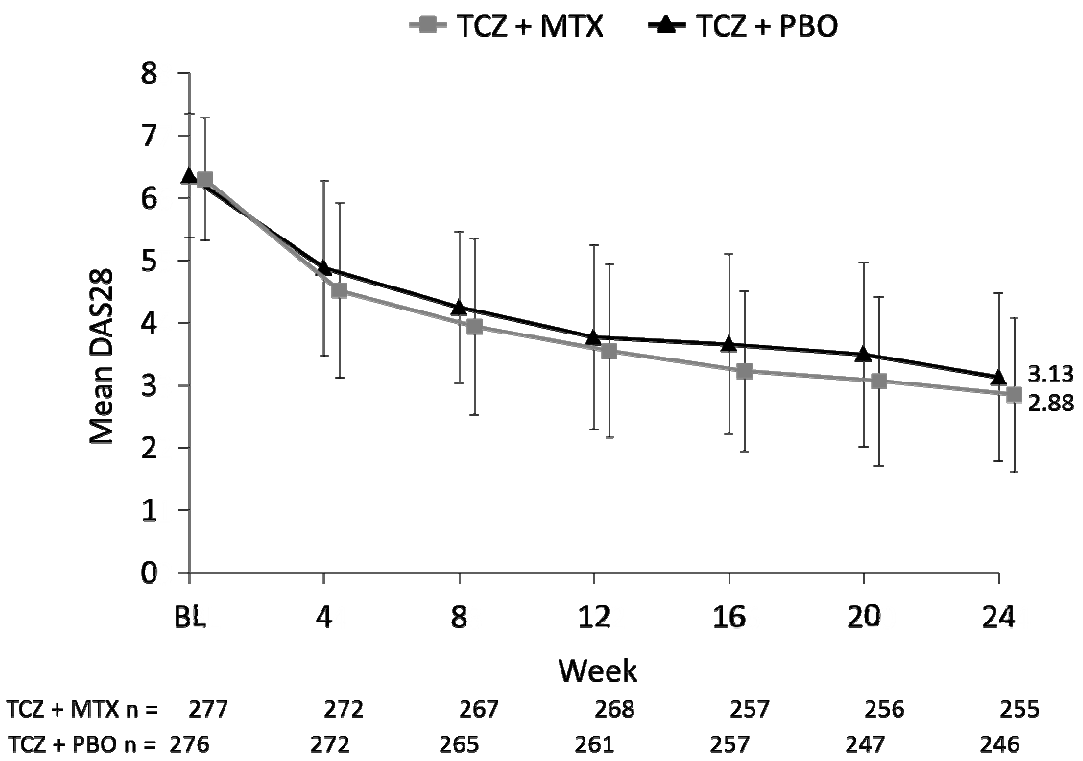


Figure S1. Mean DAS28 scores and standard deviation over time (ITT population). The TCZ + MTX series is shifted slightly to the right relative to TCZ + PBO for better readability.DAS28, disease activity score based on 28 joints. ITT, intention-to-treat.

Supplemental Table:

Table S1 HAQ-DI <0.5 and clinical remission (DAS28 <2.6) at Week 24

Patients	TCZ+MTX (N=277)	TCZ+PBO (N=276)
HAQ-DI <0.5, % (n)	29.2% (81)	25.0% (69)
DAS28 <2.6, % (n)	40.4% (112)	34.8% (96)
HAQ-DI <0.5 and DAS28 <2.6, % (n)	17.7% (49)	17.4% (48)

DAS28, Disease Activity Score based on 28 joints; HAQ-DI, health assessment questionnaire – disability index; MTX, methotrexate; PBO, placebo; TCZ, tocilizumab.