Efficacy of tocilizumab monotherapy after response to combined tocilizumab and methotrexate in patients with rheumatoid arthritis: the randomised JUST-ACT study

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Abstract

Objective

The aim of the JUST-ACT study was to assess whether the add-on effect of tocilizumab (TCZ) to background methotrexate (MTX) observed in MTX-inadequate responders with active rheumatoid arthritis (RA), would be sustained when MTX is withdrawn.

Methods

A double-blind, parallel-group, phase 3 study in biologic-naïve RA patients with a disease activity score 28 (DAS28)>3.2 despite MTX which were treated with TCZ+MTX for an initial 16-week period. Patients who at week 16 achieved low disease activity (LDA) (DAS28≤3.2) were randomised to continue with TCZ+MTX or switch to TCZ + placebo (PBO) for an additional 12 weeks. The primary endpoint was the change in DAS28-ESR from the randomisation at week 16 to week 28. Non-inferiority was confirmed if the upper limit of the two-sided 95%CI for the treatment difference between TCZ+MTX and TCZ monotherapy groups was lower than the selected non-inferiority margin of 0.6.

Results

261 patients completed the first 16 weeks of TCZ+MTX treatment and 165 were randomised (83 to TCZ+MTX and 82 to TCZ+PBO). For the primary endpoint, the adjusted treatment difference (95% CI) in mean change of DAS28-ESR was -0.06 (-0.40 to 0.27), and therefore the non-inferiority of switching to TCZ monotherapy versus continuing with TCZ+MTX was demonstrated. In both treatment groups, the percentage of patients in clinical remission from 16 to 28 weeks was similar as were the improvements in disease activity, functional disability and quality of life.

Conclusion

In MTX non-responder patients achieving LDA with TCZ+MTX, switching to TCZ monotherapy is non-inferior to continuing the combination.

Key words

tocilizumab, monotherapy, methotrexate, discontinuation, rheumatoid arthritis

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Introduction

Conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), in particular methotrexate (MTX), are and should be the first choice in the treatment of rheumatoid arthritis (RA) (1), given their acceptable clinical and functional benefits and the treatment costs of the alternative biologics. A substantial number of patients with RA, however, have an inadequate response by treat-to-target strategy and concerns also exist regarding its safety. In MTX-inadequate responders, the most international guidelines recommend adding a biologic to existing MTX because of the additional benefits.

In clinical practice, however, almost one-third of patients are taking biologics in monotherapy so as to reduce drug exposure and, in turn, avoid potential csDMARDs side effects such as MTX-related gastrointestinal, haematological and hepatic toxicity (2), and poor compliance (3). MTX toxicity may pose an inconvenience to certain patients who might prefer to discontinue MTX rather than the biological agent when the combination therapy is effective (4, 5). Indeed, in daily practice, patients treated with a TNFi often discontinue concomitant MTX without compromising the DAS28 and biologic drug survival (6), and without apparent worsening of ACR responses rates over time (7). Clinical studies, however, suggest that most biologic DMARDs are more effective in combination with MTX (4). The anti-IL-6 receptor tocilizumab (TCZ) has not been shown to have advantages when given with MTX rather than as monotherapy (8), despite small differences in secondary outcomes favouring the combination (9, 10). The novel oral janus kinase inhibitors baricitinib and tofacitinib also show modest clinical or radiological advantages over monotherapy when combined with MTX (11, 12). In a recent multinational clinical practice report, 38% of patients received TCZ as monotherapy without relevant differences with patients on MTX combination (13).

This study analyses an alternative strategy, restricted to MTX non-responder patients able to reach low disease activity (LDA) while on combination with TCZ+MTX, which in our setting continues to be the most common approach. If JUST-ACT study shows that the response to TCZ+MTX is maintained when MTX is withdrawn, these results would be useful for patients unwilling or unable to take MTX by showing an alternative to combination. Avoiding unnecessary drug exposure would reduce the risk of toxicity and cut down on compliance issues with medication.

Materials and methods

Study design and participants

JUST-ACT is a phase 3, multicentre, randomised, double-blind, parallel-group, placebo-controlled study (NCT01399697, EudraCT no. 2011-001626-15) designed to demonstrate non-inferiority, with regard to change in DAS28-ESR, of TCZ monotherapy compared with TCZ+MTX after an initial 16-week period with TCZ+MTX.

Patients with active RA inadequately controlled with prior MTX and naïve to biologic agents were enrolled at 44 sites in Spain. All patients were adults, with moderate to severe RA (DAS28 >3.2), who had been receiving MTX for ≥12 weeks, at a stable dose of ≥15 mg/week (10 mg/week if body weight <50 kg, low-grade toxicity to MTX such as nausea, or calculated glomerular filtration rate/creatinine clearance <60 ml/min) for ≥6 weeks before the study treatment, and who were willing to take oral folic acid. Oral corticosteroids (maximum dose 10 mg/day) were permitted if doses had been stable for at least 25 out of 28 days prior to study treatment, but doses could not be changed during the first 24 weeks of the study. Exclusion criteria included prior biologic treatment, any DMARD other than MTX in the month preceding (3 months for leflunomide), any investigational agent in the 4 weeks prior to screening, cellular depletion therapy, prior IV gamma globulin, plasmapheresis or Prosorba® column (in the 6 weeks prior to baseline), immunisation with a live/attenuated vaccine (in the preceding 4 weeks) or any alkylating agent. Patients who had undergone major surgery in the 8 weeks prior to screening (or planned in the 6 months following randomisation) were excluded, as were patients with rheu-

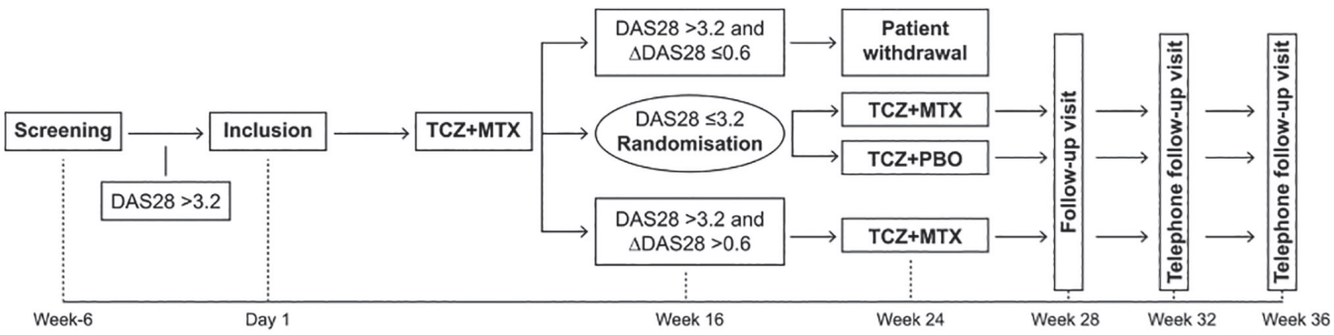

Fig. 1. Study design. DAS28, disease activity score 28; MTX, methotrexate; PBO, placebo; TCZ, tocilizumab.

matic autoimmune disease other than RA or with a history of or current inflammatory joint disease other than RA. The study was conducted in compliance with the Declaration of Helsinki, International Conference on Harmonisation Guidelines for Good Clinical Practice and local regulations. The institutional review boards/ethics committees of all participating sites approved the study, and all patients gave written informed consent before inclusion.

Treatment plan and randomisation

During the initial period of 16 weeks, all patients included in the study received TCZ (8 mg/kg IV every 4 weeks) + MTX (weekly oral dose at the patient's pre-study dose). Patients who achieved LDA at week 16 (DAS28 score ≤3.2) were randomly assigned in a 1:1 ratio to continue with TCZ (8 mg/kg IV every 4 weeks) + MTX (weekly oral dose at the patient's pre-study dose) or switch to TCZ (8 mg/kg IV every 4 weeks) + placebo (PBO) (matching the same pre-study dose of MTX) for an additional 12 weeks, until week 28. The maximum single dose allowed for TCZ was 800 mg. The dose of MTX was adjusted when necessary for safety reasons.

Patients were stratified by LDA at week 16. Allocation of patient to treatment groups was done with an interactive web response system (IWRS) on the basis of the information provided by Roche or its designee. Patients and investigators were all masked to treatment assignment. Patients who at week 16 did not reach LDA (patients with DAS28 >3.2) but experienced a moderate or good response to treatment (indicated by an improvement in DAS28 >0.6) were not randomised but continued receiving TCZ+MTX up to week 28 for safety evaluation. Patients were withdrawn from the study if they failed to achieve LDA and they did not respond to treatment during the first 16 weeks. The patients were contacted by phone for safety information at 4 and 8 weeks following the final (or early withdrawal) visit. The study design is shown in Figure 1.

Assessments

In addition to a physical exam, including vital signs and weight, and routine blood tests for haematology and biochemistry, clinical variables such as swollen and tender joint count (SJC, TJC) using 28 joints, serum levels of the acute-phase reactant C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were collected every 4 weeks. Patient's and physician's global assessments of disease (PDGA, MDGA) on a 100-mm visual analogue scale (VAS), along with the Health Assessment Questionnaire disability index (HAQ), and the 12-item short-form health survey (SF-12), were assessed at baseline and weeks 16 and 28. Disease activity was determined at baseline and weeks 16 and 28 by using the 28-joint count (DAS28)-ESR and the simplified and clinical disease activity indices (SDAI and CDAI) at baseline and week 28. LDA was defined as DAS28 ≤3.2, and the criteria for clinical remission based on DAS28, SDAI and CDAI were scores of <2.6, <3.3, and <2.8, respectively. Safety assessments included adverse events (AEs), laboratory tests, vital signs and performance status. Toxicity was graded according to the National Cancer Institute's Common Terminology (v. 4.02).

Statistical analysis

The primary endpoint was the change in DAS28-ESR from randomisation-at week 16- to week 28 between the two randomised groups. Secondary endpoints included the rate of clinical remission at week 28 based on DAS28 <2.6, CDAI <2.8 and SDAI <3.3; mean change in HAQ, SF-12, PDGA and MDGA from 16 to 28 weeks; and safety. Assuming a between-group difference in change in DAS28 of 0.07 from randomisation-at 16 to 28 weeks, a standard deviation (SD) of 1.11 and a selected non-inferiority margin of 0.6 change in DAS28 (based on published non-inferiority studies in RA) (14-16), it was estimated that a total of 158 patients (79 in each arm) needed to be randomised to achieve 90% statistical power with a two-sided α error of 0.05. Assuming 66% of the included patients would achieve DAS28 LDA at 16 weeks and 8% drop out rate, 258 patients were planned to be included to ensure the 79 patients per arm. If the upper limit of the two-sided 95% confidence interval (CI) for the difference between TCZ+MTX and TCZ monotherapy was less than the prespecified non-inferiority margin of 0.6, non-inferiority was confirmed.

The results are described for the intent-to-treat (ITT) population (all randomised patients who received at least one dose of the allocated treatment schedule and had an efficacy assessment) and the safety population (all patients who received at least one dose of medication). The between-group difference in DAS28 (primary endpoint) and in HAQ, SF-12, PDGA and MDGA from randomisation at 16 weeks to 28 weeks were analysed using an analysis of covariance (ANCOVA) model,

adjusting for the corresponding values at randomisation (week 16) as covariates. The Chi-square test was used to compare the remission rate at week 28. Missing data were not considered in the analysis.

Results

Patients

A total of 263 patients were included in the study (Fig. 2). The first patient was enrolled in August 2011, and the study concluded in March 2014. Two patients were removed from the safety population because they did not receive the study treatment. Of the 261 patients who completed the initial 16-week period with TCZ+MTX, 96 (36.7%) were not randomised, leaving 165 patients for randomisation (83 to TCZ+MTX and 82 to TCZ+PBO) and 164 for the ITT analysis after excluding one patient from the TCZ+MTX group as he did not have any evaluation of the efficacy endpoints. Over the subsequent period of 12 weeks, 80 (96.3%) patients in the TCZ+MTX group and 78 (95.1%) in the TCZ+PBO group completed the study. In the initial 16-week period and the subsequent 12-week period, patients in both groups had similar use of corticosteroids (9.6% *vs*. 8.5%; 21.7% *vs*. 22%) and the dosage was maintained stable along the study as per protocol. Demographics and disease characteristics of patients were similar between treatment groups at baseline and at the start of randomisation period (Table I). See Supplementary Table 1 for not randomised population.

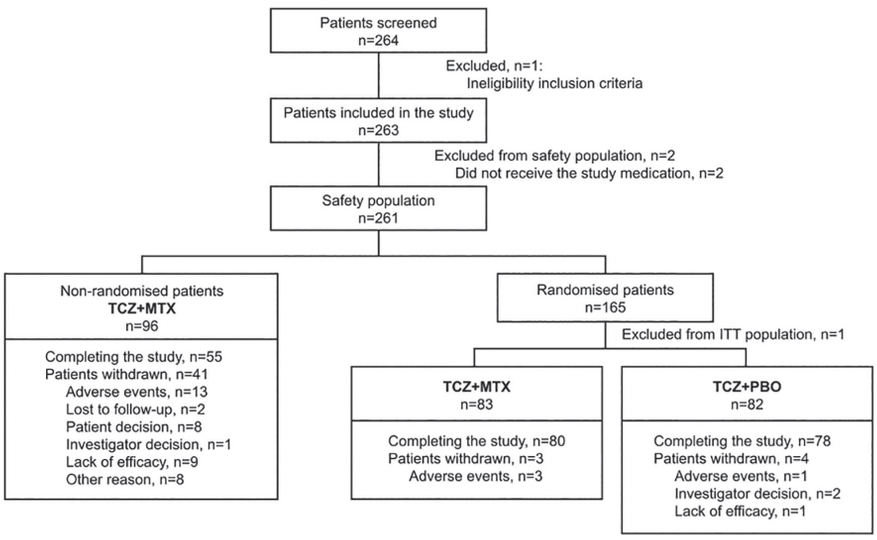

Fig. 2. Patient disposition. MTX: methotrexate; PBO: placebo; TCZ: tocilizumab.

Table I. Characteristics at baseline and week 16 (ITT population).

	TCZ+MTX (n=82)		TCZ+PBO (n=82)	
	Baseline	Week 16	Baseline	Week 16
Demographics and disease duration				
Women	62 (74.7)		65 (79.3)	
Age, years	50.2 (12.5)		51.0 (12.2)	
Disease duration, years	5.8 (5.2)		6.4 (8.2)	
Clinical outcomes				
DAS28	5.4 (1.0)	1.8 (0.8)	5.3 (1.0)	2.0 (0.8)
CDAI	28.7 (10.5)	NS	27.6 (9.9)	NS
SDAI	44. 9 (27.3)	NS	36.6 (14.3)	NS
SJC (0-28 scale)	7.4 (4.7)	0.6 (1.2)	6.9 (4.4)	0.6 (1.0)
TJC (0-28 scale)	8.9 (5.9)	1.0 (1.5)	8.9 (5.4)	1.3 (1.8)
CRP (mg/dl) in range	38 (45.8)	NS	39 (48.1)	NS
ESR (mm/h) in range	39 (47.0)	NS	38 (46.9)	NS
PDGA (0-100 VAS scale)	63.3 (19.0)	24.3 (19.8)	60.7 (20.3)	24.8 (20.1)
MDGA (0-100 VAS scale)	58.7 (15.7)	14.2 (12.4)	57.8 (15.3)	17.0 (12.9)
Patient-reported outcomes				
HAQ*	1.2 (0.7)	0.5 (0.6)	1.3 (0.8)	0.7 (0.8)
SF-12 Mental health component‡	46.2 (12.7)	51.7 (9.5)	45.5 (11.0)	51.4 (9.3)
SF-12 Physical health component‡	31.4 (10.0)	44.7 (10.1)	32.5 (8.9)	42.7 (10.0)

Data are mean (SD) or n (%). Demographic and disease duration were analysed in the safety population (TCZ+MTX, n=83; TCZ+PBO, n=82).
CDAI: clinical disease activity index; CRP: C-reactive protein; DAS28: disease activity score in 28 joints; ESR: erythrocyte sedimentation rate; HAQ: health assessment questionnaire; MDGA: physician's global assessment of disease; MTX: methotrexate; NS: not stated; PBO: placebo; PDGA: patient's global assessment of disease; SDAI, simple disease activity index; SJC, swollen joint count; TJC: tender joint count; TCZ: tocilizumab; VAS: visual analogue scale. *Lower score denotes less functional disability. ‡Higher score denotes better physical and mental quality of life.

Efficacy findings

Adding TCZ to the background MTX improved the baseline mean DAS28 at week 16 (Fig. 3A). From week 16 to week 28, DAS28 was stable in patients on TCZ+MTX and in those on TCZ monotherapy (Fig. 3A). The least squares (LS) mean change in DAS28-ESR from week 16 was 0.007 (95% CI, -0.23 to 0.24) in the TCZ+MTX group and 0.073 (95% CI, -0.16 to 0.31) in the TCZ monotherapy group.

Switching to TCZ monotherapy was non-inferior to continuing TCZ+MTX for the change in DAS28 at week 28 with and adjusted mean treatment difference of -0.06 (95% CI, -0.40 to 0.27; p=0.007). As the upper limit of the two-sided 95% CI for the difference between treatment groups was <0.6, TCZ monotherapy demonstrated non-inferiority to combination TCZ+MTX.

The percentage of patients who achieved DAS28 remission at week 28 was similar between treatment groups (p=0.328), as was the percentage of patients with CDAI remission (p=0.518) and SDAI remission (p=0.358) (Fig. 3B).

For patients in DAS28 remission at week 16, similar proportions were in sustained remission at week 28 in both the TCZ+MTX (82.4%) and TCZ+PBO groups (79.7%). We also found no significant differences between groups in

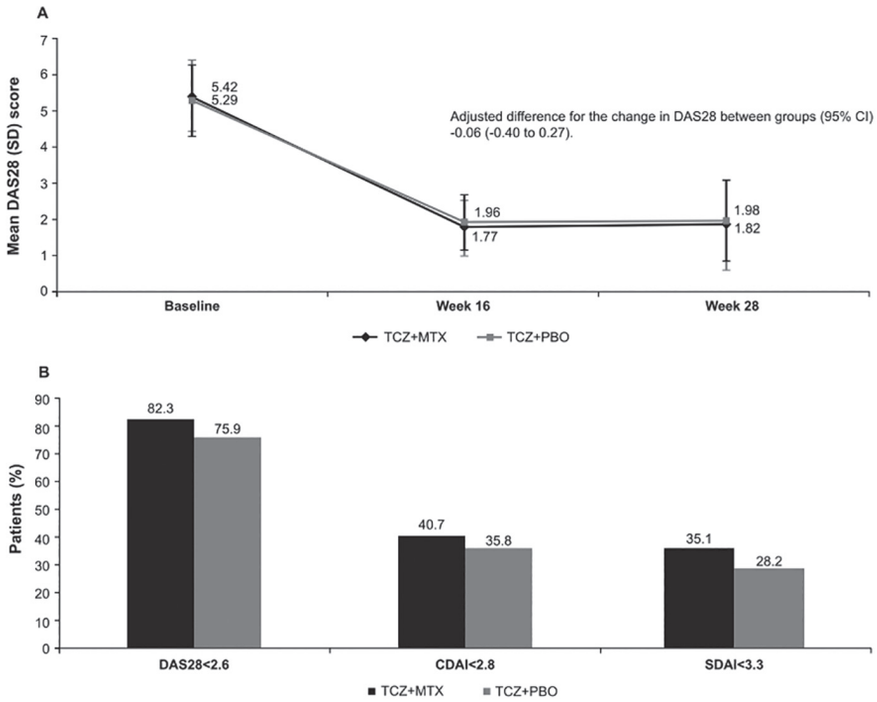

Fig. 3. (**A**) Mean change in DAS28 score from week 16 to week 28 between the two randomised groups (primary endpoint). No imputation was used for missing data (n=1 and n=3 for TCZ+MTX at week 16 and 28, respectively; n=3 for TCZ+PBO at week 28).
(**B**) Percentage of patients achieving remission at week 28. No imputation was used for missing values on DAS28 (n=3 for TCZ+MTX and n=3 for TCZ+PBO), CDAI (n=1 for TCZ+MTX and n=1 for TCZ+PBO) and SDAI (n=5 for TCZ+MTX and n=4 for TCZ+PBO). CDAI, clinical disease activity index; DAS28, disease activity score 28; MTX, methotrexate; PBO, placebo; TCZ, tocilizumab. SDAI, simplified disease activity index.

Table II. Change from week 16 in clinical and patient-reported outcomes (ITT population).

	TCZ+MTX (n=82)	TCZ+PBO (n=82)	Mean difference (95% CI)	*p*-value
Clinical outcomes				
SJC (0-28 scale)	0.14 (-0.27 to 0.56)	0.24 (-0.17 to 0.66)	-0.10 (-0.69 to 0.49)	0.736
TJC (0-28 scale)	0.56 (-0.29 to 1.42)	0.71 (-0.14 to 1.56)	-0.14 (-1.35 to 1.06)	0.812
PDGA (0-100 mm VAS scale)	1.60 (-2.98 to 6.19)	0.63 (-3.95 to 5.23)	0.96 (-5.52 to 7.46)	0.769
MDGA (0-100 mm VAS scale)	2.17 (-1.58 to 5.93)	3.39 (-0.39 to 7.17)	-1.21 (-6.57 to 4.14)	0.655
Patient-reported outcomes				
HAQ	0.06 (-0.05 to 0.16)	0.02 (-0.08 to 0.13)	0.03 (-0.12 to 0.18)	0.674
SF-12 mental health	-2.31 (-4.36 to -0.25)	-0.43 (-2.48 to 1.62)	-1.87 (-4.77 to 1.03)	0.204
SF-12 physical health	0.80 (-1.10 to 2.70)	-2.58 (-4.48 to -0.67)	3.37 (0.67 to 6.07)	0.015

ANCOVA model adjusting for the variable value at randomisation (week 16) as covariate. Treatment differences are summarised using least squares means and two-sided 95% CI.
ACR: American College of Rheumatology: ITT: intent-to-treat; HAQ: Health Assessment Questionnaire; MDGA: physician's global assessment of disease; PDGA: patient's global assessment of disease; PRO: patient report outcomes; SJC: swollen joint count; SF-12: 12-item short-form health survey; TJC: tender joint count; VAS: visual analogue scale.

mean changes from week 16 in scores of HAQ (p=0.674), SF-12 mental health (p=0.204), PDGA (p=0.769), MDGA (p=0.655), SJC (p=0.736) and TJC (p=0.812) (Table II). Only the change in SF-12 physical health composite scores from 16 to 28 weeks was significantly different between both treatment groups (p=0.015), with results at week 28 higher in favour of TCZ+MTX treatment (44.9 *vs*. 40.2). Patients experienced improvements from baseline in the SJC and TJC at week 16 or later (Table I).

Safety findings

An overview of safety is shown in Table III. Most events were of mild or moderate intensity. Urinary tract infections (5%) and back pain (5%) were the most frequent given TCZ+PBO, whereas upper respiratory tract events occurred more commonly in TCZ+MTX patients (2%). Hypertransaminasemia was experienced by 10% and 5% of patients given TCZ+MTX and TCZ+PBO, respectively. Infusion reactions occurred in 1 patient given TCZ+MTX and 2 patients given TCZ+PBO. Five patients experienced 5 serious adverse events (SAEs): 1 event of infective endocarditis given TCZ+MTX and 1 event each of infective bursitis, vertigo, staphylococcal skin infection and pneumonia given TCZ+PBO. No deaths occurred. The discontinuation rates due to AEs were low in both the TCZ+MTX (3.6%) and TCZ+PBO (1.2%) groups. Prior to randomisation, 13.3% of patients receiving TCZ+MTX discontinued because of AEs.

Discussion

The JUST-ACT study is the first blinded, controlled clinical trial that explores the strategy of MTX withdrawal after achieving LDA with combination of TCZ+MTX. The results from this study illustrate the initial efficacy of TCZ when added to background MTX and demonstrate that in patients with established RA who respond adequately to combination and achieving LDA at 16 weeks, the switch to TCZ monotherapy results in a disease control similar to that when remaining on combination therapy. The change in DAS28 12 weeks after randomiation was comparable regardless of whether MTX was discontinued. Additionally, there were no significant differences in the secondary outcomes of physical function, quality of life, and patients' and physicians' disease perceptions between patients who switched to TCZ monotherapy and those who remained on combination TCZ+MTX. Similar clinical remission rates at week 28 were also observed in both groups. Our results point to the possibility of discontinuing the accompanying MTX, thus reducing the burden of treatment,

Table III. Summary of adverse events (safety population).

	Non-randomised population (n=96)	Randomised population (n=165)	
		TCZ+MTX (n=83)	TCZ+PBO (n=82)
Total AEs	233	83	82
Patients with any AE	69 (71.9)	41 (49.4)	45 (54.9)
Patients with any SAE	11 (11.5)	1 (1.2)	4 (4.9)
Patients with any AE related to TCZ	41 (42.7)	18 (21.7)	22 (26.8)
Patients with any AE related to MTX	34 (35.4)	21 (25.3)	20 (26.8)
AEs by SOC			
Infections and infestations	31 (32.3)	15 (18.1)	18 (22.0)
Musculoskeletal and connective tissue	20 (20.8)	5 (6.0)	14 (17.1)
Hepatobiliary	20 (20.8)	9 (10.8)	4 (4.9)
Metabolism and nutrition	20 (20.8)	7 (8.4)	6 (7.3)
General disorders and administration site conditions	8 (8.3)	4 (4.8)	5 (6.1)
Gastrointestinal	19 (19.8)	2 (2.4)	4 (4.9)
Blood and lymphatic system	12 (12.5)	1 (1.2)	5 (3.7)
Skin and subcutaneous	5 (5.2)	4 (4.8)	2 (2.4)
Respiratory, thoracic and mediastinal	8 (8.3)	5 (6.0)	0 (0.0)
Vascular	6 (6.3)	2 (2.4)	2 (2.4)
Nervous system	10 (10.4)	2 (2.4)	2 (2.4)
Surgical and medical procedures	3 (3.1)	2 (2.4)	1 (1.2)
Injury, poisoning and procedural complications	6 (6.3)	3 (3.6)	0 (0.0)
Psychiatric	4 (4.2)	2 (2.4)	0 (0.0)
Renal and urinary	3 (3.1)	2 (2.4)	0 (0.0)
Reproductive system and breast	1 (1.0)	2 (2.4)	0 (0.0)
Ear and labyrinth	4 (4.2)	0 (0.0)	2 (2.4)

Data are n (%).
AE: adverse event; MTX: methotrexate; PBO: placebo; SAE: serious adverse event; SOC: system organ class; TCZ: tocilizumab.

for patients who achieve low disease activity.

These findings reinforce the conclusions from previous studies that support a similar efficacy of TCZ monotherapy compared with TCZ+MTX in MTX-inadequate responders. The ACT-RAY study showed no clinically relevant superiority of the add-on TCZ with MTX strategy over switching to TCZ monotherapy in the first 24 weeks (8). After 52 weeks, the results confirmed the sustainability of the clinical and radiographic responses with TCZ used either as monotherapy after discontinuing MTX or combined with MTX regardless of the addition of open-label csDMARDs other than MTX (9). As concluded by the authors, the possibility of introducing other csDMARDs from the first 24 weeks depending on disease activity does not allow for interpreting the 52-week results as a real analysis of TCZ as monotherapy versus combination therapy (9). However, the consistent application of this treat-to-target strategy in both study groups argues for the use of TCZ in monotherapy in patients who cannot be treated with MTX (9). By contrast, studies with the TNFi etanercept and adalimumab, conducted in either MTX-naïve or MTX-refractory patients with early or established disease, favoured the combination csDMARDs with this class of biologic agents (15, 17-20). Indeed, there is a greater probability that combination therapy with MTX results in higher ACR response rates than when either TNFi is given alone (21). The non-TNFi rituximab is also more effective when combined with MTX (22, 23).

The RETRO study provided evidence of the feasibility of discontinuing conventional or biologic DMARDs in patients in stable remission (24). Another study (CAMEO) specifically explored MTX withdrawal after 6 months of MTX plus etanercept, but patients were not randomised after achieving LDA (15). In CAMEO, the primary endpoint according to the ITT population was not met, and therefore, the non-inferiority of etanercept monotherapy *versus* ongoing etanercept plus MTX could be not claimed. Post-hoc analyses suggested comparable outcomes in monotherapy and combined therapy but the study was not initially powered for a subgroup analysis (25).

Major issues with MTX for patients with RA include intolerance and poor compliance, but also unwillingness to take it and the self-decision to reduce the medication, hence the need to find strategies to perform a monotherapy. Previous studies for TCZ have shown that monotherapy is as effective as combination therapy with MTX (21), including patient-reported outcomes (PROs) (26), so discontinuing MTX could be a feasible option in some patients with RA, particularly in intolerant or reluctant patients.

Also, the fact that the Jak inhibitors baricitinib and tofacitinib offers only modest clinical and radiological benefits over monotherapy when combined with MTX, opens up further possibilities for monotherapy.

The short period of 12 weeks on TCZ monotherapy after randomisation in JUST-ACT does not allow for a long-term evaluation of response maintenance, which may theoretically influence our results. The numerical but no statistical differences favouring patients achieving remission with combination therapy lead us to question if this would have become significant over a longer observation time. Studies of TCZ *versus* MTX show, however, no decrease in the efficacy of TCZ beyond 6 months (27-29), and a continued long-term benefit of TCZ (30, 31). Therefore, despite the very short 12-week treatment course after randomisation, our data encourage the further long-term study of TCZ monotherapy in good responders to TCZ+MTX. Recent observational data indicate that, despite comparable clinical response, TCZ retention decreases in a higher proportion among patients treated with TCZ monotherapy as compared to TCZ combined with csDMARDs after 18 months and onward (32). This point should be not ignored since some of our secondary endpoints were numerically better in the combination group.

We are conscious of the limitation of such observation period to properly conclude. Nonetheless, in the early studies of MTX tapering or discontinuation after achieving clinical stabilisation, flares occurred very early (<12 weeks) (33, 34). Whether a similar timing of flares also applies to patient on MTX biologic combination is not known. In anti-TNF plus MTX users, a 21% rate of flares at 6 months after MTX withdrawal is reported but data at earlier points is not available (6). Thus, further studies are required to infer the long-term safety and efficacy of either strategy.

Conclusion

This phase 3 study involving patients with active RA for whom treatment with MTX had previously failed showed that, once these patients respond well and reach low disease activity when adding TCZ to MTX background, remaining on combination therapy does not offer major differences over switching to TCZ as monotherapy, except for an improvement in physical self-perceived health. After 16 weeks of treatment with TCZ+MTX, patients who continue with combination show similar improvements in disease activity and physical functioning, and similar percentage of DAS28 remission than patients switching to TCZ monotherapy after 12 weeks. TCZ monotherapy may represent an alternative in such patients who cannot be treated with MTX for whom MTX holidays can be offered. Determining the best candidates for such an approach would be clinically useful in the balance of risks, benefits and cost, provided that further studies address the maintenance of long-term disease control and the potential for radiographic disease progression.

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