

## Original article

# Two-year radiographic and clinical outcomes from the Canadian Methotrexate and Etanercept Outcome study in patients with rheumatoid arthritis

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## Abstract

**Objective.** To evaluate radiographic and clinical outcomes up to 24 months in patients with RA enrolled in the Canadian Methotrexate and Etanercept Outcome study.

**Methods.** In this open-label non-inferiority trial, patients with inadequate response to MTX received etanercept plus MTX for 6 months and then were randomized to either etanercept monotherapy or continued etanercept plus MTX until 24 months. Radiographic data were analysed using the modified total Sharp score (mTSS), joint space narrowing and erosion scores. Secondary outcomes included the 28-joint DAS with ESR (DAS28-ESR), Simplified Disease Activity Index, Clinical Disease Activity Index, HAQ Disability Index (HAQ-DI) and safety.

**Results.** Two hundred five of 258 patients enrolled were randomized (98 etanercept, 107 etanercept plus MTX). At month 24, the mean increase from baseline to month 24 for the etanercept and etanercept plus MTX arms, respectively, for the mTSS were 0.4 (s.d. 1.9) and 0.0 (s.d. 1.4); for joint space narrowing, 0.1 (s.d. 0.6) and 0.0 (s.d. 0.7) and for erosion, 0.3 (s.d. 1.5) and 0.0 (s.d. 1.0). At month 24, the mean increase from month 6 mean scores/count increases for DAS28-ESR were 0.56 (s.d. 1.26) and 0.08 (s.d. 1.50); for Simplified Disease Activity Index, 4.7 (s.d. 13.1) and 0.9 (s.d. 12.5); for Clinical Disease Activity Index, 4.1 (s.d. 12.3) and 1.0 (s.d. 12.3) and for HAQ-DI, 0.20 (s.d. 0.45) and 0.02 (s.d. 0.54). Patients with DAS28-ESR low disease activity (LDA)/remission at month 6 had numerically better outcomes at month 24 than patients with moderate to high disease activity at month 6. In patients with LDA/remission at month 6, outcomes were similar at month 24 between etanercept monotherapy and etanercept plus MTX, whereas patients with moderate to high disease activity at month 6 had numerically better outcomes with etanercept plus MTX than etanercept at month 24. There were no new safety signals and serious adverse events were not different between groups.

**Conclusion.** These results support the possibility of discontinuing MTX in patients who have tolerability issues with MTX if they achieve LDA/remission.

**Trial registration:** ClinicalTrials.gov (<https://clinicaltrials.gov/>; NCT00654368).

**Key words:** rheumatoid arthritis, etanercept, methotrexate, randomized trial, radiographic outcomes, clinical outcomes.

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Submitted 10 March 2015; revised version accepted 7 August 2015

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### Rheumatology key messages

- Disease activity in RA at month 6 (low/remission vs moderate to high) predicted long-term radiographic and clinical outcomes.
- Low disease/remission after 6 months of etanercept plus MTX predicted sustained long-term benefit, with or without MTX in RA.
- RA patients with moderate to high disease at month 6 benefited from continuing on methotrexate through month 24.

## Introduction

MTX alone or in combination with other DMARDs is the most commonly used first-line therapy for patients with moderate to severe RA [1]. Patients who do not respond to or cannot tolerate MTX are treated with other non-biologic or biologic DMARDs, including TNF inhibitors (TNFi). The addition of a TNFi to MTX has been associated with improved clinical outcomes [2–7]. Approximately one-third of patients receive TNFi monotherapy (initiated as monotherapy or because of discontinuation of DMARDs, often because a low disease state has been achieved) [8, 9]. Most reimbursement criteria require that patients with active RA must fail to respond to MTX before therapy with a TNFi can be initiated. Etanercept is a TNFi that can be used as monotherapy or in combination with MTX [10].

The Canadian Methotrexate and Etanercept Outcome (CAMEO) study was a randomized, open-label, non-inferiority study that evaluated the efficacy of etanercept with or without discontinuation of MTX in biologic-naïve patients with RA who had an inadequate response to MTX. After 6 months of combination therapy with etanercept and MTX, patients were randomly assigned to discontinue MTX and continue on etanercept monotherapy or remain on combination therapy for an additional 18 months. At 12 months, patients who continued on MTX with etanercept had better clinical outcomes than those who discontinued MTX [11]. However, etanercept monotherapy provided an effective alternative to combination therapy in patients who had achieved low disease activity (LDA) by 6 months and discontinued MTX for the following 6 months. We report here the 2 year radiographic, clinical and safety outcomes (many of which were predefined outcomes of the study) in patients with RA enrolled in CAMEO.

## Patients and methods

### Study design

CAMEO was a phase 4, multicentre, open-label, randomized, non-inferiority clinical trial that was conducted at 27 sites in Canada [11]. The trial has been previously described [10]. Active RA patients with an inadequate response to MTX with or without other DMARDs who had access to etanercept under usual care were initially treated with etanercept 50 mg weekly administered subcutaneously plus steady-state MTX (minimum dose 15 mg/week) for 6 months. Patients who continued in the study were then randomized to continue etanercept 50 mg weekly plus MTX (dose adjustments were allowed for MTX post-

randomization per the clinician's standard of care) or discontinue MTX and receive etanercept monotherapy for an additional 18 months. There were no criteria for improvement or disease activity for randomization, which was performed if the investigator and patient desired to continue in the study. Study drugs were obtained in the course of routine care; no drugs were provided by the study sponsor.

This study was conducted in accordance with Canadian regulations and International Conference on Harmonization Good Clinical Practice guidelines and complied with the Helsinki Declaration. The CAMEO study, which included results reported at 1 year and these results reported at 2 years, was approved by Research Review Board, Inc. (Richmond Hill, Ontario, Canada) and hospital and university sites where required. Written informed consent was provided by all patients before initiation of any study-related procedures. This study was registered under ClinicalTrials.gov identifier NCT00654368.

### Patients

Adults ( $\geq 18$  years of age) with active RA despite stable MTX therapy for  $>12$  weeks were eligible to enrol in CAMEO. Patients met the 1987 American Rheumatism Association criteria for RA [12], experienced RA symptoms for  $\geq 6$  months, had active disease at baseline (defined as three or more swollen joints and DAS28-ESR  $\geq 3.2$ ), had not received prior therapy with a biologic, had an indication for etanercept per the approved product monograph [10], were able to continue MTX and had received a dose of  $\geq 15$  mg/week (or 10 mg/week if intolerant) for  $\geq 12$  weeks with a stable dose for  $\geq 4$  weeks before the baseline visit and were able to receive etanercept with private or public insurance. Key exclusion criteria included prior biologic treatment or any investigational therapy within 4 weeks of initiation of study medication or during the study period.

### Outcome measures

Efficacy outcomes, including the 28-joint DAS with ESR (DAS28-ESR), Simplified Disease Activity Index (SDAI; *post hoc* analysis) [13], Clinical Disease Activity Index (CDAI; *post hoc* analysis) [13], tender joint counts based on 28 joints, swollen joint counts based on 28 joints and patient-reported disability using the HAQ Disability Index (HAQ-DI) [14], were assessed at baseline (study entry) and 6, 12, 18 and 24 months and at study discontinuation in patients who terminated early. The primary endpoint was the difference between treatment groups in the change in DAS28-ESR from 6 month randomization to 12 months

and has been previously reported [11]. Radiographic outcomes (X-rays of the hands and feet) were assessed at baseline and at 12 and 24 months or at the time of discontinuation. X-rays were evaluated centrally by a single blinded reader. Modified total Sharp score (mTSS) [15], joint space narrowing (JSN) and erosion scores were determined. Rates of radiographic progression (mTSS, JSN and erosion scores) were calculated using each patient's duration from baseline to last X-ray. Safety outcomes included all adverse events, serious adverse events, serious infectious events and events of interest (herpes zoster, tuberculosis, malignancy and death).

### Statistical considerations

Selection of sample size has been previously reported [11]. This 2 year analysis included multiple subgroup analyses with small sample sizes, which decreased the level of precision of the estimates. Endpoints collected at time points after the primary non-inferiority objective at month 12 were summarized descriptively to assess long-term efficacy and safety. In a pre-specified analysis, data were stratified by response at the time of randomization at month 6 [LDA/remission (DAS28-ESR <3.2) vs moderate to high disease activity (MHDA; DAS28-ESR  $\geq$ 3.2)] for efficacy analyses. Efficacy outcomes were analysed using the intent-to-treat population, defined as all enrolled patients who were randomized to a treatment arm. Missing data were imputed using last observation carried forward (LOCF) for continuous variables, non-responder imputation for categorical variables and multiple imputation [16] for sensitivity analyses. End of study was defined as month 24 for patients who completed the study or the last visit for patients who discontinued early. Analyses employing multiple imputations reassigned the premature termination visit to the nearest per-protocol visit. Statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA).

Radiographic outcomes were a secondary objective of the protocol and statistical analyses are descriptive only. The rate of radiographic progression was calculated using the actual time between X-rays, in years. Radiographic progression was defined as mTSS >0 at any time post-baseline based on evaluations by a single reviewer.

*Post hoc* analyses included SDAI and CDAI remission and LDA and the ACR/EULAR Boolean definition of remission; components used to calculate *post hoc* analyses were collected per the protocol. Additional *post hoc* analyses to examine the association of DAS28-ESR status at month 6 on sustained LDA/remission were based on logistic regression adjusted for treatment, reimbursement type, duration of disease and region. Probabilities were calculated from adjusted odds ratios (ORs) resulting from the logistic regression [17]. Sensitivity analyses assessing the predictive value of DAS28-ESR status at month 6 included analysis of variance and a receiver operating characteristic curve (results not shown). Covariates that were examined as possible predictors of response included sex; race; age; duration of RA; RF status; baseline and month 6 DAS28-ESR; baseline BMI; baseline

HAQ-DI score; baseline mTSS score; prior MTX use (dose and duration); prior use of biologics, corticosteroids, NSAIDs, DMARDs or analgesics; region and reimbursement type. The logistic regression and multivariable models were for descriptive, exploratory purposes only. At the 1 year interim analysis [11], it was determined that HAQ-DI was imbalanced between the two treatment arms at baseline as well as at month 6 randomization. Analysis of covariance was used on the HAQ-DI scores after month 6, adjusting for baseline differences [18].

## Results

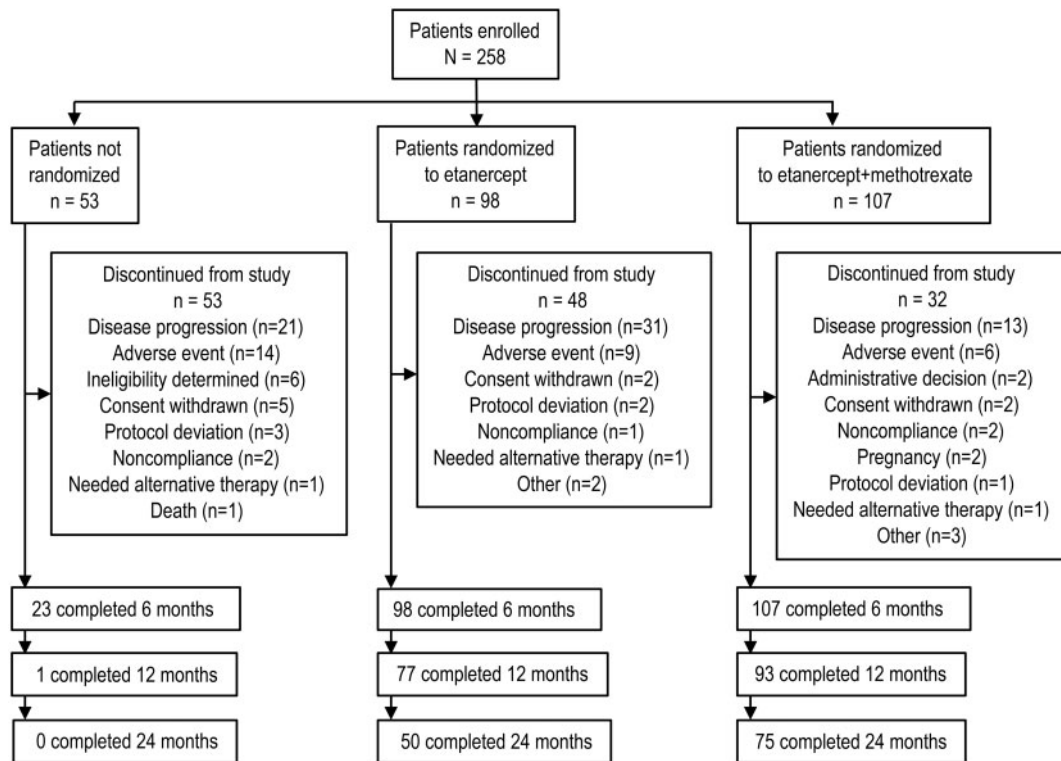
### Patients

A total of 258 patients enrolled in the study and received etanercept in addition to their stable MTX. Of these, 205 patients were randomized at month 6 to either etanercept (n=98) or etanercept plus MTX (n=107). Demographic and clinical characteristics of the patient population have been previously reported [11]. One hundred seventy-one (82.9%) randomized patients completed 12 months and 125 (61.0%) completed 24 months in the study. Patients in the etanercept monotherapy arm had a higher rate of discontinuation from the study (49.0%) than patients receiving etanercept plus MTX (29.9%) (Fig. 1). The most common reason for discontinuing from the study in both treatment arms and in patients who were not randomized was disease progression (loss of response, insufficient response or flare). Of the 107 patients randomized to etanercept plus MTX, 5 (4.7%) discontinued MTX prior to study completion and 74.8% continued to be prescribed etanercept after study completion. Three (3.1%) patients randomized to etanercept monotherapy stayed on MTX for >1 year after randomization and 81.6% continued to be prescribed etanercept. The median dose of MTX for patients on etanercept plus MTX was 20 mg/week at baseline and months 6, 12 and 24.

### Radiographic outcomes through month 24

Radiographic outcomes were analysed for all patients within the intent-to-treat population who had at least one post-baseline radiographic measurement (Table 1). Seven patients had no X-ray data (four in the etanercept arm and three in the etanercept plus MTX arm). Patients in both treatment arms had similar time between baseline and final X-rays with a median of 2.0 years, with minimums of slightly more than 6 months (due to premature terminations) and maximums of 2.3 years. The percentage of patients with an mTSS, JSN or erosion score of zero was slightly higher in the etanercept plus MTX arm than the etanercept arm at month 24 (Table 1). Three patients on etanercept monotherapy had rapid progression (worsening of mTSS >5/year); two were observed within the first 12 months and one was observed at month 15 (premature termination from study). Overall, most patients in both treatment arms (60.6% on etanercept, 64.4% on etanercept plus MTX) had no change in mTSS from baseline to month 24/end of study (Fig. 2). Rates of

Fig. 1 Patient disposition



ETN: etanercept.

radiographic progression (mTSS, JSN and erosion scores) were higher in patients with MHDA at month 6 than in patients with LDA/remission at month 6 (supplementary Table S1, available at *Rheumatology* Online). The subgroup of patients with LDA/remission at month 6 had similar radiographic outcomes between treatment arms at months 12 and 24, whereas the subgroup of patients with MHDA at month 6 had slightly better radiographic outcomes post-randomization for the etanercept plus MTX arm compared with the etanercept monotherapy arm.

#### Clinical outcomes at month 24

DAS28-ESR, SDAI and CDAI scores and number of tender joints increased slightly in both treatment arms from month 6 (randomization) to month 24/end of study; however, the magnitude of change was less in patients receiving etanercept plus MTX compared with patients on etanercept monotherapy (Table 2). Results were consistent with both LOCF and the sensitivity analysis of multiple imputation (data not shown). The number of swollen joint counts decreased slightly from month 6 to month 24/end of study for the etanercept plus MTX arm, but increased in the etanercept arm. An analysis of the subgroup of patients who had achieved DAS28-ESR LDA/remission at randomization (month 6) showed that similar proportions of patients sustained LDA/remission through month 24 in both treatment arms (Fig. 3). For patients in this subgroup

who were in remission (DAS28-ESR <2.6) at month 6, the probability of sustaining LDA or remission out to month 24 was 82%, adjusting for treatment [OR 0.7 (95% CI 0.3, 1.8)], disease duration, reimbursement type and region.

For the subgroup of patients who achieved LDA/remission at month 6, mean DAS28-ESR, SDAI and CDAI changes from baseline were not different between the two treatment arms out to month 24 (supplementary Table S2 and supplementary Fig. S1, available at *Rheumatology* Online). The proportion from this subgroup continuing with LDA or remission at any assessment between 6 and 24 months was also similar between the two treatment arms. In contrast, for the subgroup of patients who did not achieve LDA/remission but were in MHDA at month 6, mean DAS28-ESR, SDAI and CDAI scores increased in patients on etanercept monotherapy but decreased in patients on etanercept plus MTX from month 6.

#### Patient-reported outcomes at month 24

On average, the HAQ-DI remained the same with combination therapy and increased slightly with etanercept monotherapy from 6 to 24 months, with a mean change from month 6 of 0.20 (s.d. 0.45) in the etanercept arm and 0.02 (s.d. 0.54) in the etanercept plus MTX arm. The change in mean HAQ-DI scores from month 6 to month 24/end of study was similar in patients with LDA/remission and those with MHDA at month 6 (supplementary Table



**TABLE 1** Radiographic measures through month 24/end of study (ITT analysis set; LOCF imputation)

| Radiographic measure  | ETN (n = 94)  | ETN + MTX (n = 104) |
|---|---------------|---------------------|
| mTSS <sup>a</sup> , mean score (s.d.)                         |               |                     |
| Baseline  | 37.9 (55.7)   | 38.2 (50.1)         |
| Month 12  | 39.7 (57.0)   | 38.7 (50.6)         |
| Month 24  | 38.3 (56.1)   | 38.2 (50.1)         |
| mTSS change from baseline to month 24, mean score (s.d.)      | 0.4 (1.9)     | 0.0 (1.4)           |
| mTSS score of zero at month 24, n (%)                         | 11 (11.7)     | 13 (12.5)           |
| mTSS progression <sup>b</sup> at month 24, n (%)              | 23 (24.5)     | 19 (18.3)           |
| Rate of progression of mTSS >5/year, n (%)                    | 3 (3.2)       | 0                   |
| JSN <sup>c</sup> , mean score (s.d.)                          |               |                     |
| Baseline  | 21.1 (27.8)   | 22.9 (26.9)         |
| Month 12  | 21.9 (28.2)   | 23.2 (27.2)         |
| Month 24  | 21.2 (27.9)   | 23.0 (26.9)         |
| JSN change from baseline to month 24, mean score (s.d.)       | 0.1 (0.6)     | 0.0 (0.7)           |
| JSN score of zero at month 24, n (%)                          | 13 (13.8)     | 17 (16.3)           |
| JSN progression <sup>b</sup> at month 24, n (%)               | 12 (12.8)     | 9 (8.7)             |
| Erosion <sup>d</sup> , mean score (s.d.)                      |               |                     |
| Baseline  | 16.8 (29.4)   | 15.3 (25.0)         |
| Month 12  | 17.7 (30.3)   | 15.5 (25.3)         |
| Month 24  | 17.0 (29.7)   | 15.3 (25.0)         |
| Erosion change from baseline to month 24, mean score (s.d.)   | 0.3 (1.5)     | 0.0 (1.0)           |
| Erosion score of zero at month 24, n (%)                      | 21 (22.3)     | 27 (26.0)           |
| Erosion progression <sup>b</sup> at month 24, n (%)           | 20 (21.3)     | 16 (15.4)           |
| Radiographic progression, mean rate of change per year (s.d.) |               |                     |
| mTSS <sup>a</sup>   | 0.202 (1.190) | -0.006 (0.734)      |
| JSN <sup>b</sup>  | 0.070 (0.525) | 0.050 (0.356)       |
| Erosion <sup>c</sup>  | 0.132 (0.925) | -0.055 (0.595)      |

<sup>a</sup>Score ranges from 0 (no disease) to 448. <sup>b</sup>Progression was defined as a worsening >0. <sup>c</sup>Score ranges from 0 (no disease) to 168. <sup>d</sup>Score ranges from 0 (no disease) to 280. ETN: etanercept; ITT: intent-to-treat; JSN: joint space narrowing; LOCF: last observation carried forward; mTSS: modified total Sharp score.

S2, available at *Rheumatology* Online). The proportions of patients with improvement  $\geq 0.22$  in the HAQ-DI and with a normal HAQ-DI (score  $\leq 0.5$ ) at month 24/end of study were numerically greater in patients with LDA/remission compared with patients with MHDA at month 6.

### Safety

Overall, 81.4% of all patients reported an adverse event, 13.6% reported a serious adverse event and 4.7% reported a serious infectious event during the entire study (Table 3). Most events were mild or moderate in severity.

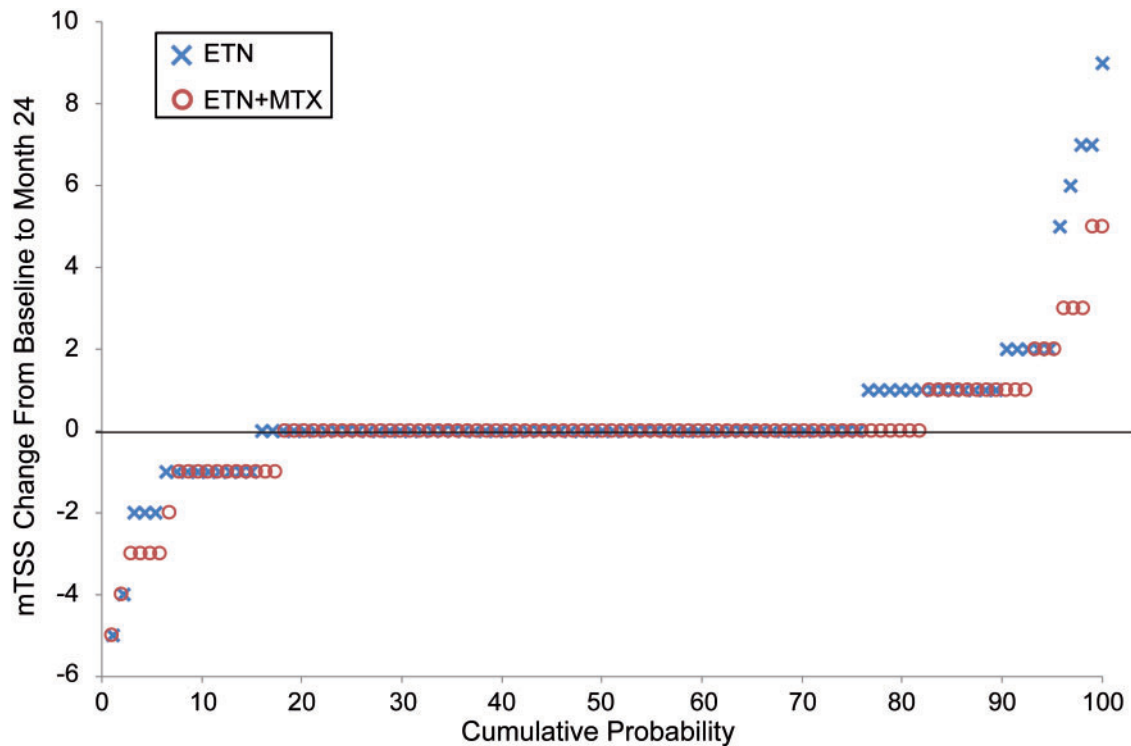
One death was reported; the patient died of sepsis before the 6-month randomization and the event was considered by the investigator to be related to etanercept. No tuberculosis was reported. No differences were seen between the two treatment arms.

### Discussion

The overall purpose of CAMEO was to evaluate the clinical and radiographic effects of MTX withdrawal after 6 months of combination therapy with etanercept plus MTX for up to 2 years in patients who had previously had an inadequate response to MTX (and usually other additional DMARDs) in a usual care study. At month 12 of the study, non-inferiority of etanercept monotherapy to combination therapy with etanercept plus MTX was not demonstrated [11]. A pre-specified analysis based on response at month 6 (when patients were randomized to continue on MTX plus etanercept or receive etanercept only) showed that patients who had achieved LDA/remission at month 6 had greater clinical and radiographic improvements than those who remained in MHDA at month 6. The results from CAMEO did not reveal any demographic or clinical characteristics that were predictive of response, including sex, race, duration of RA, RF status, baseline and month 6 DAS28-ESR, BMI, baseline HAQ score, baseline mTSS score, prior MTX dose and duration, prior use (number and types) of RA medications (including non-TNFi biologics, corticosteroids, NSAIDs, DMARDs or analgesics), region and reimbursement type. Data on smoking status and presence of ACPA were not collected in the study and could not be included in the analyses of response predictors. Analyses that are adequately powered for investigation of predictors of response warrant further research.

Combination therapy with etanercept and MTX appeared to lead to moderately better clinical outcomes than etanercept monotherapy overall. However, the pre-planned analysis based on disease status at month 6 clearly showed that patients with DAS28-ESR LDA/remission at month 6 could discontinue MTX and sustain their clinical status up to month 24. This observation may be useful if MTX is withdrawn for any reason, such as tolerability, side effects, compliance or other clinical issues after treatment with MTX plus etanercept.

A strength of this study was that it mirrored real-world use of etanercept. At study inception, patients had demonstrated an inadequate response to MTX, and etanercept was then added at the standard dosing regimen, which is consistent with current treatment guidelines [19]. Many patients had been exposed to several DMARDs: 44% of patients on etanercept and 47% of patients on etanercept plus MTX had received two or more DMARDs prior to participating in the study. Although combination therapy with MTX and a TNFi has been shown to lead to improved clinical outcomes [2–7], clinicians or their patients may nevertheless wish to discontinue MTX. Registries suggest that approximately one in three patients are not on a background DMARD [20–22], so the data from this study help to demonstrate that withdrawal

**Fig. 2** Change in mTSS change from baseline to month 24 for each patient

ETN: etanercept; mTSS: modified total Sharp score.

**TABLE 2** Month 6 to month 24/end of study clinical outcomes (ITT analysis set; LOCF imputation)

| Clinical outcome | ETN (n = 98), mean (s.d.) |             |                       | ETN + MTX (n = 107), mean (s.d.) |             |                       |
|------------------|---------------------------|-------------|-----------------------|----------------------------------|-------------|-----------------------|
|                  | Month 6                   | Month 24    | Change (month 24 – 6) | Month 6                          | Month 24    | Change (month 24 – 6) |
| DAS28-ESR        | 3.44 (1.42)               | 4.03 (1.57) | 0.56 (1.26)           | 3.47 (1.47)                      | 3.55 (1.63) | 0.08 (1.50)           |
| SDAI score       | 13.1 (11.1)               | 17.7 (14.4) | 4.7 (13.1)            | 13.6 (11.4)                      | 14.7 (13.9) | 0.9 (12.5)            |
| CDAI score       | 13.0 (11.2)               | 17.1 (13.9) | 4.1 (12.3)            | 12.9 (11.2)                      | 14.2 (13.8) | 1.0 (12.3)            |
| TJC28            | 4.9 (6.2)                 | 6.0 (6.5)   | 1.0 (5.6)             | 4.9 (6.5)                        | 5.0 (6.4)   | 0.1 (5.7)             |
| SJC28            | 3.4 (4.0)                 | 4.6 (5.0)   | 1.2 (4.3)             | 3.6 (3.9)                        | 3.4 (4.3)   | -0.2 (4.3)            |

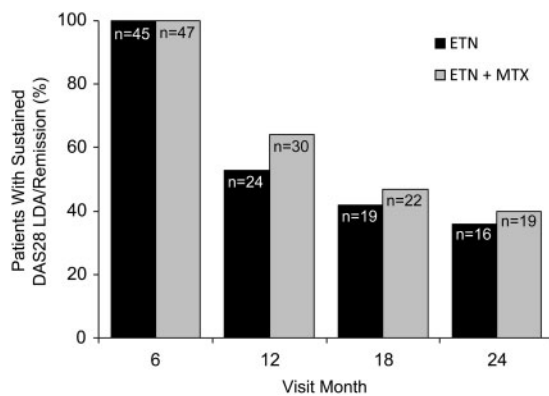
CDAI: Clinical Disease Activity Index; ITT: intent-to-treat; LOCF: last observation carried forward; SDAI: Simplified Disease Activity Index; SJC28: swollen joint count based on 28 joints; TJC28: tender joint count based on 28 joints.

of MTX in those not in LDA/remission may not be optimal for long-term benefit. In addition, the entry criteria for CAMEO were less restrictive than most clinical trials and allowed most patients who would qualify to receive etanercept in Canadian practice, so the results may be generalizable to many patients with active RA. The 24 month duration of the study allowed for long-term evaluation of the sustainability of response to combination therapy and monotherapy.

A limitation of the study was the small sample size for subgroup analyses, which decreased the level of precision of the estimates. In addition, X-rays were performed at baseline, month 12 and month 24, but not at the time of

randomization at month 6 (although no difference would be expected at month 6 since all patients had been on etanercept plus MTX and the rate of X-ray progression would be expected to be very low over the first 6 months). X-rays were evaluated by a single blinded reader, which may have resulted in less precision of the estimates of radiographic progression compared with using two readers. X-rays did not differ between disease states as has been previously shown with TNFi agents, but the results were likely underpowered. The two randomized treatment arms had different premature discontinuation rates, suggesting that data are not missing at random in this study. An LOCF approach was applied

**Fig. 3** Sustained DAS28-ESR LDA/remission through month 24 in patients with DAS28-ESR LDA/remission at month 6



DAS28-ESR: 28-joint DAS with ESR; ETN: etanercept; LDA: low disease activity.

**TABLE 3** Summary of safety (full analysis set; as observed)

| Patients reporting an AE | Nonrandomized (n = 53) | ETN (n = 98) | ETN + MTX (n = 107) | All patients (n = 258) |
|--------------------------|------------------------|--------------|---------------------|------------------------|
| Any AE, n (%)            | 32 (60.4)              | 86 (87.8)    | 92 (86.0)           | 210 (81.4)             |
| SAE, n (%)               | 7 (13.2)               | 11 (11.2)    | 17 (15.9)           | 35 (13.6)              |
| SIE <sup>a</sup> , n (%) | 3 (5.7)                | 4 (4.1)      | 5 (4.7)             | 12 (4.7)               |
| AE of interest, n (%)    |                        |              |                     |                        |
| Herpes zoster            | 0                      | 2 (2.0)      | 1 (0.9)             | 3 (1.2)                |
| Malignancy <sup>b</sup>  | 2 (3.8)                | 3 (3.1)      | 3 (2.8)             | 8 (3.1)                |
| Death                    | 1 (1.9)                | 0            | 0                   | 1 (0.4)                |

<sup>a</sup>SIEs included pneumonia, bronchopneumonia, cellulitis, device-related infection, diverticulitis, infectious pleural effusion, lung abscess, sepsis and urinary tract infection. <sup>b</sup>Malignancies included basal cell carcinoma, metastatic lung cancer, squamous cell lung carcinoma, non-Hodgkin lymphoma, prostate cancer, squamous cell carcinoma and transitional cell carcinoma. AE: adverse event; ETN: etanercept; SAE: serious adverse event; SIE: serious infectious event.

with a sensitivity analysis using multiple imputation on the data that were missing because of premature discontinuation. Results were similar using the two approaches, therefore only the LOCF analysis is reported here. Since lack of efficacy was a common reason for discontinuation, the estimates presented here may be biased toward worsening disease.

## Conclusion

In conclusion, this study assessed the long-term impact of withdrawing MTX in a real-world, randomized controlled trial with 2 years of follow-up in patients on a stable combination of a biologic agent and MTX. Non-inferiority between etanercept and etanercept plus MTX was not achieved at month 12. Withdrawal of MTX

resulted in slightly elevated disease activity and disease progression at month 24, particularly in patients with MHDA at the time of withdrawal. These results suggest that if MTX withdrawal is contemplated following combination therapy with etanercept plus MTX, patients in a state of LDA or remission may benefit. In general, two drugs had small numeric mean improvements over monotherapy and this appeared to be driven by the patients in MHDA at month 6.

## Acknowledgements

We thank the clinical investigators of the CAMEO study, including Nabil Attie, Milton Baker, Murray Baron, William Bensen, Louis Bessette, Andrew Chow, Isabelle Fortin, Michel Gagné, Eric Grant, Mark Hazeltine, Anna Jaroszynska, Raman Joshi, Algis Joviasis, Arthrus Karasik, Majed Khraisi, Juris Lazovskis, Janet Markland, Timothy McCarthy, Saeed Shaikh, Ali Shickh, Hyman Tannenbaum and John Watterson. We also thank Edward Mancini of Amgen and Julia R. Gage on behalf of Amgen for assistance with writing the manuscript. Medical writing assistance was funded by Amgen.

**Funding:** This work was supported by Amgen Canada and Pfizer Canada.

**Disclosure statement:** E.C.K. has received grants and/or honoraria for participating on advisory boards from AbbVie, Amgen, AstraZeneca Pharmaceuticals, Bristol-Meyers Squibb, Centocor, F. Hoffmann-LaRoche, Genzyme, Merck & Co, Novartis Pharmaceuticals, Pfizer, UCB, Genentech and Nycomed and for his role as speaker from AbbVie, Bristol-Meyers Squibb, F. Hoffmann-LaRoche, Merck & Co, Pfizer and UCB. A.V. is a former employee of Amgen Canada. K.P.-C. is an employee of Amgen Canada and has stock options in Amgen. J.E.P. has received grants and/or honoraria for her roles as investigator and for participating on advisory boards from AbbVie, Amgen, Actelion Pharmaceuticals, AstraZeneca Pharmaceuticals, Bristol-Meyers Squibb, GlaxoSmithKline, F. Hoffmann-La Roche, Janssen Pharmaceuticals, Novartis Pharmaceuticals, Pfizer and UCB. J.C.T. has received grants and/or honoraria for his roles as investigator and consultant from Amgen, Pfizer, AbbVie, Bristol-Meyers Squibb, Centocor, Merck & Co, F. Hoffmann-La Roche and UCB. M.P.-C. is an employee and stock owner of Amgen. B.H. has received honoraria for advisory boards and consultancies as well as received grants/research support from AbbVie, Amgen, Bristol-Meyers Squibb, Celgene, Janssen, Pfizer, Roche and UCB.

## Supplementary data

Supplementary data are available at *Rheumatology Online*.

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