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## EXTENDED REPORT

## Efficacy and safety of ascending methotrexate dose in combination with adalimumab: the randomised CONCERTO trial

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## ABSTRACT

**Objective** CONCERTO was a randomised, double-blind, parallel-armed study of methotrexate (MTX) in combination with adalimumab to assess whether an increasing trend of efficacy and decreased safety exists when increasing MTX dose in patients with early rheumatoid arthritis (RA).

**Methods** Early, biologic and MTX-naïve RA patients (N=395) were evenly randomised to open-label adalimumab (40 mg every other week) plus weekly blinded 2.5, 5, 10 or 20 mg MTX for 26 weeks. Clinical, radiographic and functional outcomes were analysed using two-sided linear trend tests or one-way analysis of covariance.

**Results** Statistically significant increasing trends were observed in the proportion of patients achieving the primary endpoint, 28-joint count disease activity score with C reactive protein (DAS28(CRP)) <3.2 (42.9%, 44.0%, 56.6% and 60.2% for 2.5, 5, 10 or 20 mg/week MTX, respectively), DAS28(CRP) <2.6 and American College of Rheumatology 50/70/90 responses with increasing doses of MTX in combination with adalimumab. No statistical differences in minimal clinically important differences in physical function were detected. Statistically significant trends for achieving low disease activity and remission were demonstrated with increasing MTX dose by validated clinical indices; differences comparing 10 and 20 mg MTX were minimal. Adalimumab serum concentrations increased with ascending dose up to 10 mg MTX. More patients experienced infectious adverse events with increasing MTX dose.

**Conclusions** Increasing doses of MTX in combination with adalimumab demonstrated a statistically significant trend in improved clinical outcomes that mimicked the adalimumab pharmacokinetic profile. In early RA patients initiating adalimumab combination therapy, efficacy of 10 and 20 mg/week MTX appeared equivalent.

## INTRODUCTION

Methotrexate (MTX) is the generally recommended first-line, disease-modifying antirheumatic drug (DMARD) for the treatment of patients with rheumatoid arthritis (RA) by the European League Against Rheumatism (EULAR)<sup>1</sup> and the American College of Rheumatology (ACR)<sup>2</sup> as it has been shown to be efficacious, with an acceptable toxicity profile, and is cost effective.<sup>3 4</sup> A folate analogue, MTX's mode of action in RA is not entirely clear,

although increasing adenosine levels and reducing pro-inflammatory cytokines seem to play a more predominant role than inhibition of cellular proliferation.<sup>4 5</sup>

The dose of MTX as monotherapy can range from 7.5 to 25 mg/week, depending on national guidelines and physician's preference. A systematic literature review of MTX monotherapy has recommended initial treatment with 10–15 mg orally with dose increases to 20–30 mg/week if needed and tolerated.<sup>6</sup> Parenteral administration of MTX has been suggested to be more effective with fewer gastrointestinal adverse events (AEs) in patients with suboptimal response or intolerance to oral MTX.<sup>7 8</sup> Older literature has suggested that MTX toxicity is dose-dependent and low dose MTX monotherapy treatment can be effective.<sup>9–13</sup> However, no randomised controlled trials have explored the minimally effective dose of MTX in a group of patients when used in combination with a tumour necrosis factor (TNF) inhibitor to balance risk–benefit; this dose may well be different than previously proposed minimally effective monotherapy doses.

Antagonists to TNF, including adalimumab, are recommended for patients who continue to have active disease following non-biologic medication optimisation with DMARDs. Additionally, for patients with high disease activity and risk factors associated with poor outcomes, including anticyclic citrullinated peptide (anti-CCP) antibodies, rheumatoid factor (RF) and erosive disease, recommendations include earlier initiation of biologic treatment to reduce joint damage and functional decline.<sup>1 2</sup> Anti-TNFs in combination with MTX have been shown to be effective in significantly improving clinical manifestations of RA, with the goal of achieving remission or low disease activity (LDA).<sup>14–19</sup>

The combination of adalimumab+MTX has been shown to be more effective than adalimumab monotherapy in groups of patients. Adalimumab peak serum concentrations are typically reached about 5 days after subcutaneous administration of a single 40 mg dose. Subcutaneous administration of 40 mg adalimumab every other week in RA patients can achieve mean steady-state trough concentrations ranging from 5 µg/mL without concomitant MTX to 8–9 µg/mL with concomitant MTX.<sup>20</sup> Optimising adalimumab combination therapy to achieve disease control should identify the minimal

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efficacious dose of MTX in combination with adalimumab. The CONCERTO trial evaluated ascending doses of MTX in combination with adalimumab to explore the dose response of MTX and the risk–benefit profiles of these doses of MTX in combination with adalimumab in patients with early, active RA.

## METHODS

### Patients

Eligible patients were  $\geq 18$  years of age with RA defined by either the 1987 revised ACR classification<sup>21</sup> or the new ACR/EULAR diagnostic criteria.<sup>22</sup> Patients must have had a disease duration  $< 1$  year, 28-joint count disease activity score (DAS28) based on C reactive protein (CRP)  $\geq 3.2$ , swollen joint count (SJC)  $\geq 6$  of 66 joints assessed, tender joint count (TJC)  $\geq 8$  of 68 joints assessed, CRP  $\geq 1.5$  mg/dL or erythrocyte sedimentation rate  $\geq 28$  mm/h, and  $\geq 1$  bony erosion, RF positivity or anti-CCP antibody positivity. Patients were excluded if previously exposed to a biologic DMARD, including adalimumab, previous treatment with MTX or therapy with  $> 1$  DMARD.

### Study design

CONCERTO (ClinicalTrials.gov Identifier: NCT01185301) was a randomised, double-blind, parallel-arm, multicentre study to determine the dose response of MTX in combination therapy with adalimumab in patients with early, active RA. The study was conducted from October 2010 to September 2012. Patients from 64 study sites were stratified based on their consent to optional pharmacogenetic analysis and randomised 1:1:1:1 using an interactive voice response system to oral MTX at 2.5, 5, 10 or 20 mg weekly; all patients received subcutaneous open-label 40 mg adalimumab every other week, and 5 mg/week folic acid. Patients randomised to the 20 mg MTX treatment group were started at 10 mg/week and escalated by 2.5 mg every 2 weeks to 20 mg/week by 8 weeks. If MTX intolerance/toxicity was suspected, blinded MTX dose reduction of 5 mg, including during the escalation period, could be performed, although effectively reduced only for the 10 and 20 mg/week treatment groups. Temporary MTX discontinuation followed by re-introduction/re-escalation of MTX was allowed if the issue was resolved within 4 weeks. x-Rays were collected at baseline and week 26. The study was reviewed by an independent IRB and followed good clinical practice and ethical principles that have their origin in the Declaration of Helsinki; all patients provided informed consent.

### Clinical, functional and radiographic assessments

Clinical and functional disease assessments were measured at baseline and weeks 2, 4, 8, 12, 16, 20 and 26. The primary efficacy endpoint was the proportion of patients achieving DAS28 (CRP)  $< 3.2$  at week 26. Secondary variables included the proportions of patients achieving the following criteria: DAS28 (CRP)  $< 2.6$ ; ACR20/50/70/90 response; clinical disease activity index (CDAI) LDA and remission ( $\leq 10$  and 2.8, respectively); simplified disease activity index (SDAI) LDA and remission ( $\leq 11$  and 3.3, respectively); minimal clinically important differences in function (Health Assessment Questionnaire Disability Index (HAQ-DI) change  $\leq -0.22$  from baseline); and normal function (HAQ-DI  $< 0.5$ ) over time. The modified total Sharp score (mTSS) was used to assess the proportion of patients with radiographic non-progression ( $\Delta$ mTSS  $\leq 0.5$  from baseline). For the purposes of this study, comprehensive disease control (CDC) was defined as the simultaneous achievement of HAQ-DI  $< 0.5$ ,  $\Delta$ mTSS  $\leq 0.5$  and DAS28(CRP)  $< 3.2$  (CDC<sub>LDA</sub>) or  $< 2.6$  (CDC<sub>REM</sub>), respectively, although DAS28(CRP)  $< 3.2$  or  $< 2.6$

are not validated LDA or remission criteria. Samples for pharmacokinetic analysis and antiadalimumab antibodies (AAA) were collected prior to dose at each study visit. A patient was considered AAA+ if at least one sample had measured AAA greater than 20 ng/mL within 30 days after an adalimumab dose.

### Safety assessments

AEs were collected by MedDRA V.15.0; physical examination (including vital signs) and laboratory data were assessed by the investigator for seriousness, severity and relationship to study medications. AEs commonly attributed to MTX intolerance/toxicity were defined according to 18 prespecified AEs found in the MTX prescribing information. Treatment-emergent AEs were defined as any AE with an onset on or after the first dose of study drug and up to 70 days after last dose.

### Statistical analyses

Week 26 combination therapy dose response was tested using the two-sided Cochran-Armitage Trend test. Percentages of responders were compared among treatment groups using non-responder imputation. Changes in continuous variables were compared among treatment groups using analysis of covariance adjusted for baseline. Missing values for continuous variables were imputed using last observation carried forward. Analysis of safety included all patients who received at least one dose of adalimumab. Mean change in laboratory variables were compared between treatment groups using one-way analysis of variance.

## RESULTS

### Baseline patient demographics, disease characteristics and patient flow

Of 395 patients with early RA enrolled in CONCERTO, 358 (90.6%) completed 26 weeks of combination therapy. Baseline demographics and disease characteristics were evenly balanced between the four treatment groups (table 1). The CONCERTO population had a mean disease duration of less than 4 months, with high disease activity shown by a mean baseline DAS28 (CRP) of  $6.02 \pm 0.97$ , HAQ-DI of  $1.57 \pm 0.67$  and multiple poor prognostic markers.

Discontinuations were 15.3%, 7.0%, 6.1% and 9.2% of patients receiving 2.5, 5, 10 and 20 mg MTX+adalimumab, respectively (figure 1). AEs were reported as the primary reason for 8/37 discontinuations, generally equal between groups. Of patients who discontinued early, lack of efficacy was a likely cause for some withdrawals, although this information was not specifically captured.

### Clinical and patient-reported efficacy following 26-week therapy

Following 26 weeks of adalimumab plus MTX, a statistically significant trend in the proportion of patients achieving DAS28 (CRP)  $< 3.2$ , the primary endpoint, was found with increasing MTX dose (42.9%, 44.0%, 56.6% and 60.2% of patients in the 2.5, 5, 10 and 20 mg MTX groups, respectively;  $p=0.005$ ; figure 2A). Week 26 pairwise comparisons of 2.5 and 5 mg MTX to 20 mg MTX were statistically significant ( $p=0.016$ , OR=2.02 (95% CI 1.14 to 3.56);  $p=0.023$ , OR=1.93 (95% CI 1.09 to 3.39), respectively). Differences in the proportion of patients with DAS28(CRP)  $< 3.2$  comparing 2.5–10, 5–10 or 10–20 mg MTX were not statistically different at week 26. Response measured by DAS28(CRP)  $< 2.6$  also demonstrated a statistically significant increasing trend with increasing MTX dose in combination with adalimumab from week 16 onward

**Table 1** Patient demographics and baseline disease characteristics

	ADA+2.5 mg MTX (N=98)	ADA+5 mg MTX (N=100)	ADA+10 mg MTX (N=99)	ADA+20 mg MTX (N=98)
Age, years	52.0±13.2	49.7±13.1	52.1±12.9	53.8±14.4
Age distribution, n (%)				
<65 years	84 (85.7)	89 (89.0)	85 (85.9)	77 (78.6)
≥65 years	14 (14.3)	11 (11.0)	14 (14.1)	21 (21.4)
Female, n (%)	70 (71.4)	78 (78.0)	78 (78.8)	74 (75.5)
RA duration, years	0.35±0.84	0.29±0.22	0.33±0.30	0.31±0.41
Concomitant medications, n (%)				
NSAIDs	69 (70.4)	61 (61.0)	69 (69.7)	59 (60.2)
Corticosteroids	31 (31.6)	27 (27.0)	39 (39.4)	31 (31.6)
TJC68	27.4±14.7	29.0±15.4	26.4±14.7	25.8±13.7
SJC66	18.9±12.7	19.7±13.2	16.4±11.7	17.1±11.8
TJC28	16.6±6.4	17.0±6.9	14.7±6.4	15.4±6.2
SJC28	12.7±6.6	13.0±6.3	11.1±6.3	11.8±5.7
PGA disease activity (VAS 0–100 mm)	66.5±15.4	68.4±16.0	65.6±15.7	64.7±18.1
PtGA disease activity (VAS 0–100 mm)	70.6±21.7	71.6±20.4	67.7±20.2	65.5±22.9
PtGA pain (VAS 0–100 mm)	70.0±20.2	69.2±18.7	66.3±18.5	66.5±20.2
mTSS	9.8±12.9	8.6±8.9	10.8±13.0	10.6±12.9
Estimated annual mTSS progression*	28.0	29.7	32.6	34.0
ESR (mm/h)	41.7±15.4	50.3±23.4	42.9±18.9	47.7±20.9
CRP (mg/dL)	2.0±2.5	2.7±3.0	2.3±3.2	2.5±3.6
ACPA positive, n (%)	76 (77.6)	77 (77.0)	81 (81.8)	81 (82.7)
RF positive, n (%)	85 (86.7)	83 (83.0)	82 (82.8)	80 (81.6)
DAS28(CRP)†	6.10±0.92	6.22±0.94	5.86±0.97	5.91±1.01
SDAI	45.3±14.2	46.5±14.6	41.4±15.0	42.7±14.9
CDAI	43.3±13.6	43.8±13.8	39.1±13.5	40.2±12.8
HAQ-DI	1.49±0.74	1.57±0.62	1.62±0.67	1.58±0.65

Data are mean±SD unless indicated otherwise.

\*Calculated by dividing mean baseline mTSS by mean disease duration at baseline.

†N values=96, 98, 95 and 97 for ADA+2.5, 5, 10 and 20 mg, respectively.

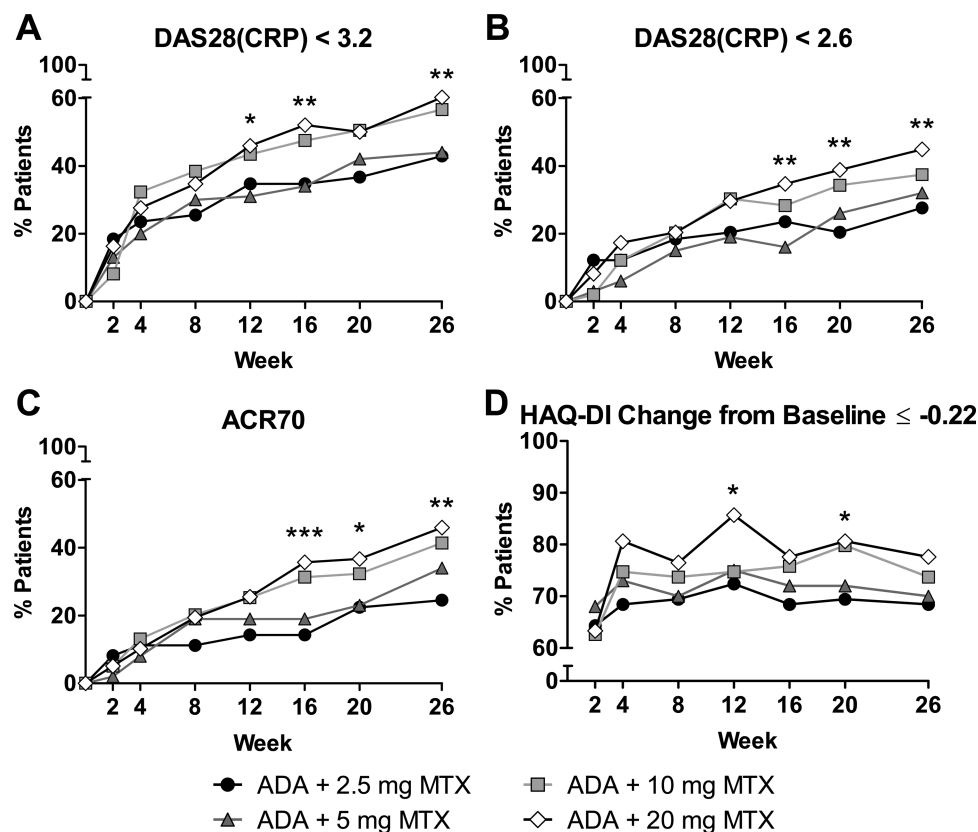
ACPA, anticitrullinated peptide antibody; ADA, adalimumab; CDAI, clinical disease activity index; CRP, C reactive protein; DAS28, 28-joint count disease activity score; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire Disability Index; mTSS, modified total Sharp score; MTX, methotrexate; NSAIDs, non-steroidal anti-inflammatory drugs; PGA, physician's global assessment; PtGA, patient's global assessment; RA, rheumatoid arthritis; RF, rheumatoid factor; SDAI, simple disease activity index; TJC, tender joint count; SJC, swollen joint count; VAS, visual analogue scale.

( $p<0.01$ ; figure 2B). Week 26 CRP mean changes from baseline were similar across treatment groups and did not influence differences in response (data not shown).

Following 26 weeks of treatment, ACR50/70/90 all showed statistically significant increasing trends in the proportion of patients achieving response with increasing MTX dose ( $p<0.05$ ), observed as early as week 12 (figure 2C and online supplementary figure S1). There was no statistical difference in

the numbers of patients from the 2.5, 5, 10 and 20 mg MTX groups achieving a minimal clinically important decrease in HAQ-DI (68.4%, 70.0%, 73.7% and 77.6%, respectively) or week 26 mean HAQ-DI change from baseline ( $-0.72$ ,  $-0.71$ ,  $-0.78$  and  $-0.82$ , respectively); clinically meaningful improvements were noted by the validated measures of CDAI and SDAI, were similar to DAS28(CRP) results. Statistically significant increasing

**Figure 1** Patient disposition. Primary reasons for discontinuation are listed.



**Figure 2** Clinical and functional efficacy following 26 weeks of open-label adalimumab in combination with different doses of MTX. Proportion of patients achieving DAS28(CRP) <3.2 (A), <2.6 (B), ACR70 (C) and change from baseline HAQ-DI  $\leq -0.22$  (D). DAS28, 28-joint disease activity score; CRP, C reactive protein; ACR, American College of Rheumatology; HAQ-DI, Health Assessment Questionnaire Disability Index; ADA, adalimumab; MTX, methotrexate. Missing values were imputed using non-responder imputation. \*, \*\* and \*\*\* denote statistical significance at the 0.05, 0.01 and 0.001 levels, respectively.

trends with increasing MTX dose were observed for the proportion of patients achieving CDAI LDA ( $p=0.026$ ) and remission ( $p=0.022$ ), occurring by 12 weeks and maintained to week 26 (figure 3A,B). Similarly, increasing trends in percentage of patients achieving SDAI LDA were observed at weeks 16, 20 and 26 with ascending MTX doses ( $p<0.05$ ; figure 3C); SDAI remission trends were observed from week 12 to 26 ( $p\leq 0.01$ ; figure 3D). The 10 and 20 mg MTX dose groups plus adalimumab displayed nearly identical proportion of patients achieving LDA and remission through 26 weeks.

Adalimumab steady-state trough serum concentrations mimicked the clinical outcomes observed with MTX dose, increasing with ascending MTX dose up to 10 mg MTX. Mean trough concentrations ( $\pm$ SD) at week 26 were 4.4 (5.2), 5.7 (4.9), 6.5 (4.4) and 6.9 (3.4) with ascending MTX, respectively (figure 3E). Adalimumab concentrations comparing patients treated with either 10 or 20 mg were similar over time. The per cent of patients with at least one AAA+ sample were 21%, 13%, 6% and 6% for the 2.5, 5, 10 and 20 mg MTX dose groups, respectively.

Patient's global assessment (PtGA) and physician's global assessment (PGA) with ascending MTX dose were not statistically significant ( $p=0.177$  and  $p=0.083$ , respectively); mean PGA at week 26 was 23.0, 23.1, 17.4 and 16.4 for 2.5, 5, 10 and 20 mg MTX, respectively (see online supplementary figure S2A,B). Rapid PGA improvement of  $\sim 40\%$  within 2 weeks was observed regardless of MTX dose. Week 26 PtGA of pain differences were statistically significant with increasing MTX dose (mean scores 33.7, 34.6, 28.5 and 24.0 for 2.5, 5,

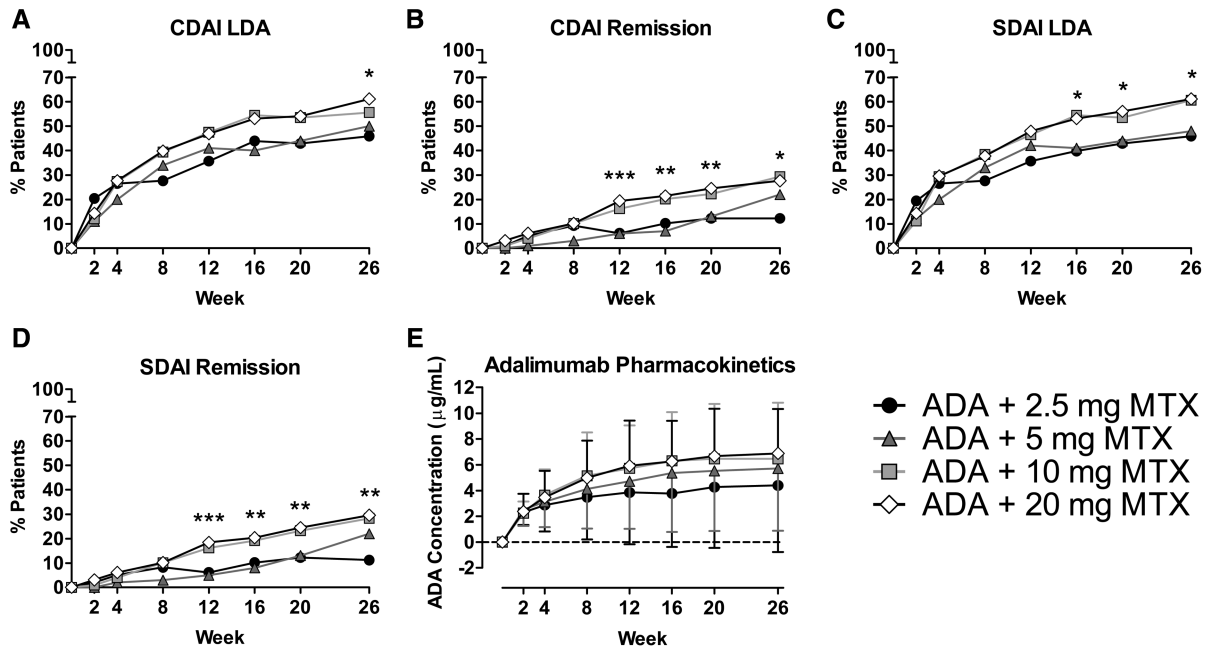
10 and 20 mg MTX, respectively,  $p=0.031$ ; online supplementary figure S2C). Patient global treatment satisfaction, measured by the Treatment Satisfaction Questionnaire for Medication V1.4, improved from week 2 to 26 in treatment groups receiving 10 or 20 mg MTX, whereas patients on 2.5 or 5 mg MTX were less satisfied with their treatment (see online supplementary figure S2D). Overall improvement from baseline in TJC68 and SJC66 ranged from 71.0% to 74.6%, respectively, with minor differences between treatment groups (see online supplementary figure S2E,F).

### Radiographic non-progression and CDC following combination therapy

All MTX dosing groups in combination with adalimumab demonstrated similar low degree of radiographic progression measured by mTSS (figure 4A,B). Week 26 mean changes in mTSS from baseline were 0.9, 0.3, 0.4 and 0.2 for the 2.5, 5, 10 and 20 mg MTX doses, respectively; removal of a single outlier within the 2.5 mg MTX group lowered the group  $\Delta$ mTSS mean to 0.4.

CDC of RA encompasses the reduction of inflammation, preservation of physical function and prevention of structural damage. As with other clinical measures, the proportion of patients achieving CDC<sub>LDA</sub> and CDC<sub>REM</sub> improved with increasing doses of MTX in combination with adalimumab at week 26 ( $p=0.023$  and 0.020, respectively; figure 4C,D). Approximately a third of patients receiving adalimumab+20 mg MTX achieved CDC<sub>LDA</sub> compared with  $\sim 20\%$  of patients in the lower MTX groups; similarly, 26.5% of patients achieved





**Figure 3** Clinical LDA, remission and adalimumab pharmacokinetics following 26-week treatment with adalimumab in combination with ascending MTX doses. Proportion of patients achieving LDA or remission measured by CDAI (A and B, respectively) or SDAI (C and D, respectively). Mean adalimumab trough concentrations ( $\pm$ SD) over time (E). CDAI, clinical disease activity index; LDA, low disease activity; SDAI, simplified disease activity index; ADA, adalimumab; MTX, methotrexate. Missing values were imputed using non-responder imputation. \*, \*\* and \*\*\* denote statistical significance at the 0.05, 0.01 and 0.001 levels, respectively.

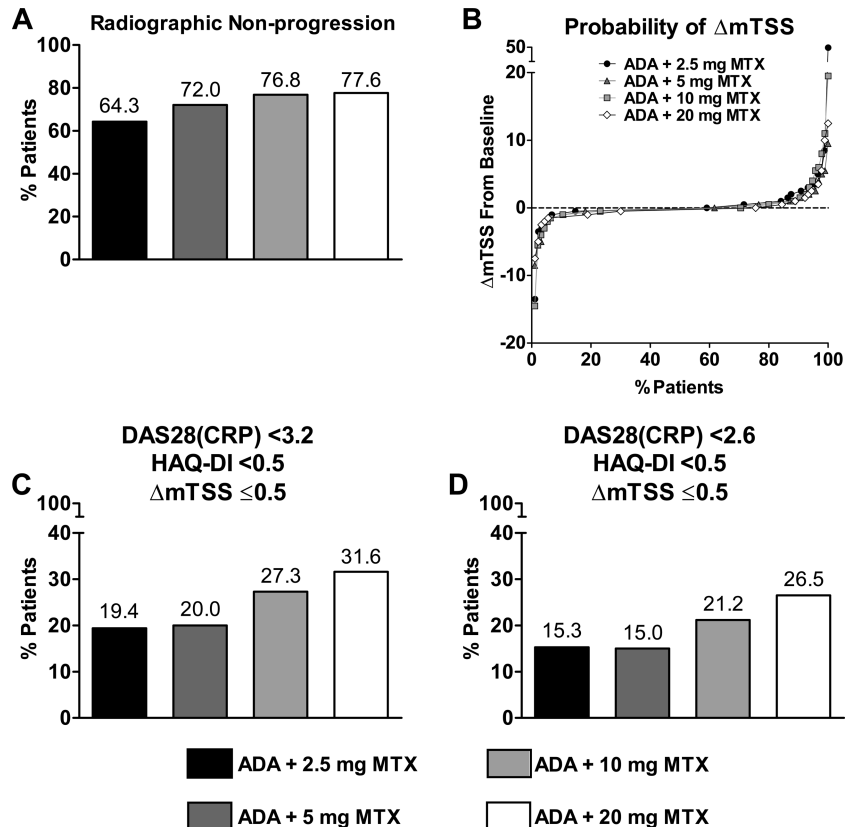
CDC<sub>REM</sub> in the 20 mg MTX group compared with ~15% of patients in the lower MTX groups.

**Safety assessments**

Overall, 254/395 (64%) of patients experienced an AE (62%–69% comparing groups) (table 2). No opportunistic infections,

tuberculosis, lymphomas, other malignancies (other than one incidence of non-melanoma skin cancer), demyelinating disorder or deaths were observed through week 26. No obvious AE trends were observed with increasing MTX dose in combination with adalimumab with the exception of infectious AEs and abnormal hair loss; however, serious infections were not

**Figure 4** Radiographic and composite measures of disease following 26 weeks of adalimumab + MTX treatment. Proportion of patients with no radiographic progression ( $\Delta$ mTSS  $\leq$ 0.5) (A), probability of mTSS change from baseline (B), comprehensive disease control using DAS28(CRP) <3.2 (C) and comprehensive disease control using DAS28(CRP) <2.6 (D). ADA, adalimumab; MTX, methotrexate; mTSS, modified total Sharp score; DAS28, 28-joint disease activity score; CRP, C reactive protein; HAQ-DI, Health Assessment Questionnaire Disability Index. Missing values were imputed using non-responder imputation.



**Table 2** Safety results following 26-week treatment, n (%)

Treatment emergent events*	ADA+2.5 mg MTX (N=98)	ADA+5 mg MTX (N=100)	ADA+10 mg MTX (N=99)	ADA+20 mg MTX (N=98)	Total (N=395)
Any AE	61 (62.2)	59 (59.0)	66 (66.7)	68 (69.4)	254 (64.3)
AE leading to discontinuation	3 (3.1)	0	2 (2.0)	4 (4.1)	9 (2.3)
Serious AE	5 (5.1)	2 (2.0)	3 (3.0)	7 (7.1)	17 (4.3)
Severe AE	3 (3.1)	2 (2.0)	5 (5.1)	6 (6.1)	16 (4.1)
Infectious AE	20 (20.4)	17 (17.0)	24 (24.2)	34 (34.7)	95 (24.1)
Serious infections	0	2 (2.0)	0	0	2 (0.5)
Common AEs†					
Nausea and/or vomiting	7 (7.1)	5 (5.0)	13 (13.1)	8 (8.2)	33 (8.4)
Stomach pain/discomfort	6 (6.1)	6 (6.0)	7 (7.1)	12 (12.2)	31 (7.8)
Nasopharyngitis	3 (3.1)	6 (6.0)	6 (6.1)	11 (11.2)	26 (6.6)
Headache	4 (4.1)	6 (6.0)	5 (5.1)	9 (9.2)	24 (6.1)
Abnormal hair loss	1 (1.0)	5 (5.0)	6 (6.1)	8 (8.2)	20 (5.1)
Unexplained diarrhoea	3 (3.1)	6 (6.0)	6 (6.1)	3 (3.1)	18 (4.6)
Dizziness	4 (4.1)	0	6 (6.1)	4 (4.1)	14 (3.5)
Injection site reaction	1 (1.0)	5 (5.0)	5 (5.1)	3 (3.1)	14 (3.5)
Upper respiratory tract infection	2 (2.0)	2 (2.0)	3 (3.0)	5 (5.1)	12 (3.0)
Excessive fatigue and/or malaise	4 (4.1)	1 (1.0)	3 (3.0)	2 (2.0)	10 (2.5)
Skin rash and/or hives	1 (1.0)	3 (3.0)	3 (3.0)	2 (2.0)	9 (2.3)
Oral ulcers	0	1 (1.0)	5 (5.1)	2 (2.0)	8 (2.0)
Fever and/or chills	0	1 (1.0)	3 (3.0)	0	4 (1.0)
Chronic dry cough	0	1 (1.0)	1 (1.0)	1 (1.0)	3 (0.8)
Unexplained visual change	0	0	2 (2.0)	1 (1.0)	3 (0.8)
Abnormal sweating	1 (1.0)	1 (1.0)	1 (1.0)	0	3 (0.8)
Tinnitus	1 (1.0)	0	1 (1.0)	1 (1.0)	3 (0.8)
Conjunctivitis	0	0	0	2 (2.0)	2 (0.5)
Skin pigment changes	0	0	1 (1.0)	1 (1.0)	2 (0.5)
Unintended weight loss	1 (1.0)	1 (1.0)	0	0	2 (0.5)
Nose bleed	1 (1.0)	0	0	0	1 (0.3)
Liver function tests‡					
ALT, mean change from baseline, IU/L	2.6	2	6.6	4	3.9
ALT >1.5×ULN, n (%)	4 (4.1)	4 (4.0)	5 (5.0)	7 (7.1)	20 (5.1)
ALT >3.0×ULN, n (%)	2 (2.0)	0	1 (1.0)	1 (1.0)	4 (1.0)
AST, mean change from baseline, IU/L	3.6	1.6	4.6	2.4	3
AST >1.5×ULN, n (%)	4 (4.1)	2 (2.0)	3 (3.0)	4 (4.1)	13 (3.3)
AST >3.0×ULN, n (%)	2 (2.0)	0	0	0	2 (0.5)
Anaemia	2 (2.0)	0	1 (1.0)	2 (2.0)	5 (1.3)
Leucopenia	1 (1.0)	1 (1.0)	0	0	2 (0.5)
Platelet count (× 10 <sup>9</sup> /L)	276.7±73.3	264.5±73.3	258.9±78.5	251.9±73.8	262.8±75.0
Platelet count, mean change from baseline (× 10 <sup>9</sup> /L,±SD)	-38.5±78.8	-48.5±70.7	-40.1±61.8	-51.0±76.7	-44.6±72.0

\*Any treatment emergent event is defined as any AE with an onset date on or after the day of the first ADA dose through 70 days after the last ADA dose.

†Infections, nausea and/or vomiting, stomach pain/discomfort, abnormal hair loss, unexplained diarrhoea, dizziness, excessive fatigue and/or malaise, skin rash and/or hives, oral ulcers, fever and/or chills, chronic dry cough, unexplained visual change, abnormal sweating, tinnitus, conjunctivitis, skin pigment change, unintended weight loss, and nose bleed were prespecified to be assessed at each study visit for relation to MTX, although presented data are irrespective of relation to MTX.

‡N values for liver function tests = 85, 92, 94 and 90 for 2.5, 5, 10 and 20 mg MTX, respectively.

ADA, adalimumab; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; MTX, methotrexate; ULN, upper limit of normal.

related to MTX dose. Among infectious AEs, the number of patients experiencing nasopharyngitis increased with ascending MTX dose. Mean change from baseline in hepatic enzymes occurred similarly in all dose groups. The finding of alanine aminotransferase level >1.5×upper limit of normal (ULN) at any point in the study occurred in 5.1% of patients; 3.3% experienced aspartate aminotransferase elevation >1.5×ULN.

## DISCUSSION

Patients with early, active RA, especially with the presence of poor risk factors and rapid radiographic progression, are known to be at increased risk of irreversible joint damage and

functional decline<sup>23 24</sup> requiring intensive treatment. Early intervention with disease-modifying pharmacotherapy has been shown to significantly control disease activity more effectively than delaying treatment for even a short period of time<sup>25</sup> preventing consequences of long-term disease inflammation, radiographic progression and subsequent loss of function. According to the EULAR guidelines and ACR recommendations, MTX is the appropriate first-line DMARD for treating active RA based on its established efficacy and safety;<sup>26–28</sup> however, the intensive use of MTX monotherapy achieves ACR/EULAR-defined satisfactory disease control in only approximately a third of patients and two-thirds of patients require more active therapy which

may include a biologic DMARD in combination with MTX.<sup>1 2</sup> Despite the clinical use of the combination of a biologic DMARD and MTX over the past 15 years, CONCERTO is the first blinded, controlled clinical trial that has explored the risk-benefit of different doses of MTX in patients with early, active RA initiating anti-TNF combination therapy with multiple poor prognostic factors, commonly seen in practice. Determining the optimal starting MTX dose, in a group of patients, to maximise efficacy without increasing safety signals should provide insight into the optimal management of these patients. CONCERTO demonstrated a statistically significant trend of improved efficacy with increasing dose of MTX from 2.5 to 20 mg/week. Surprisingly, similar clinical, radiographic and functional responses were observed in patients treated with 10 and 20 mg MTX per week in combination with 40 mg/week adalimumab. The proportions of patients achieving clinically meaningful outcomes seemed to be still increasing at the end of the 26-week study, suggesting that differences between treatment groups could be more pronounced with longer treatment. The clinical outcomes observed in CONCERTO, including ACR response rates, were consistent with other adalimumab studies in patients with early RA.<sup>16 29 30</sup>

Low adalimumab serum concentrations have previously been shown to decrease treatment efficacy;<sup>31</sup> examining different controlled doses of MTX with a constant adalimumab dose has not been done previously. Dosage of MTX at 10 and 20 mg/week tended to trend together with respect to achieving changes in DAS28(CRP), ACR responses, CDAI, and SDAI; weekly 2.5 and 5 mg MTX doses also trended together. Adalimumab serum concentrations were highest with 10 and 20 mg/week of MTX, mimicking their clinical responses. These findings are consistent with previous findings of reduced clearance of adalimumab when administered with concomitant MTX.<sup>20 32</sup> Not assessing higher doses of MTX may be a study limitation; however, the similarities in adalimumab serum concentrations and AAA comparing 10 and 20 mg MTX, and data demonstrating oral MTX plasma pharmacokinetics plateau above a dose of 15 mg,<sup>33</sup> suggest otherwise. Disease measures of both functional and radiographic outcomes did not demonstrate statistical differences between treatment groups suggesting that any dose of MTX in combination with adalimumab is sufficient to control these two important aspects of RA treatment.

With respect to safety, the incidence of infections, but not serious infectious events, were increased with increasing MTX dose; this finding may have been the result of increased adalimumab serum levels, although previous analyses have not shown correlations between adalimumab concentration and infections.<sup>31 34</sup> These studies, however, were not designed to directly assess the safety of different doses of MTX in combination with a fixed dose of adalimumab as was CONCERTO.

CONCERTO examined different doses of MTX in biologic-naive patients with early, aggressive disease, the results of which may not be completely generalisable to patients with extensive previous DMARD exposure or longer disease durations. Adalimumab and 10 or 20 mg/week MTX provided equivalent meaningful improvements in disease outcomes. In general, MTX and adalimumab in biologic-naive patients with early RA demonstrated robust and dose-dependent clinical responses with increasing doses of MTX through 26 weeks. These results may be specific to adalimumab. Further studies of MTX in combination with other biologic DMARDs may be necessary to see if these results are generalisable or adalimumab-specific. Patient-reported treatment satisfaction, clinical efficacy and

pharmacokinetics suggest that for patients initiating adalimumab combination therapy, the optimal starting dose may be lower than previously assumed without a significant difference in the benefit-risk profile of 10 and 20 mg/week of MTX. These novel findings suggest that treating physicians may consider 10 mg of MTX a week when deciding which dose of MTX to choose in conjunction with anti-TNF therapy and presents an opportunity to lower MTX dosage in patients with RA.

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## REFERENCES

- Smolen JS, Landewe R, Breedveld FC, *et al*. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis* 2014;73:492–509.
- Singh JA, Furst DE, Bharat A, *et al*. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2012;64:625–39.
- Weinblatt ME. Efficacy of methotrexate in rheumatoid arthritis. *Br J Rheumatol* 1995;34(Suppl 2):43–8.
- Swierkot J, Szechinski J. Methotrexate in rheumatoid arthritis. *Pharmacol Rep* 2006;58:473–92.
- Cutolo M, Bisso A, Sulli A, *et al*. Antiproliferative and antiinflammatory effects of methotrexate on cultured differentiating myeloid monocytic cells (THP-1) but not on synovial macrophages from patients with rheumatoid arthritis. *J Rheumatol* 2000;27:2551–7.
- Visser K, Katchamart W, Loza E, *et al*. Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative. *Ann Rheum Dis* 2009;68:1086–93.
- Braun J, Kastner P, Flaxenberg P, *et al*. Comparison of the clinical efficacy and safety of subcutaneous versus oral administration of methotrexate in patients with active rheumatoid arthritis: results of a six-month, multicenter, randomized, double-blind, controlled, phase IV trial. *Arthritis Rheum* 2008;58:73–81.
- Mouterde G, Baillet A, Gaujoux-Viala C, *et al*. Optimizing methotrexate therapy in rheumatoid arthritis: a systematic literature review. *Joint Bone Spine* 2011;78:587–92.
- Furst DE, Koehnke R, Burmeister LF, *et al*. Increasing methotrexate effect with increasing dose in the treatment of resistant rheumatoid arthritis. *J Rheumatol* 1989;16:313–20.
- Mielants H, Veys EM, Van der Straeten C, *et al*. The efficacy and toxicity of a constant low dose of methotrexate as a treatment for intractable rheumatoid arthritis: an open prospective study. *J Rheumatol* 1991;18:978–83.

- 11 Cronstein BN. Low-dose methotrexate: a mainstay in the treatment of rheumatoid arthritis. *Pharmacol Rev* 2005;57:163–72.
- 12 Yamanaka H, Inoue E, Tanaka E, *et al*. Influence of methotrexate dose on its efficacy and safety in rheumatoid arthritis patients: evidence based on the variety of prescribing approaches among practicing Japanese rheumatologists in a single institute-based large observational cohort (IORRA). *Mod Rheumatol* 2007;17:98–105.
- 13 Takeuchi T, Yamanaka H, Ishiguro N, *et al*. Adalimumab, a human anti-TNF monoclonal antibody, outcome study for the prevention of joint damage in Japanese patients with early rheumatoid arthritis: the HOPEFUL 1 study. *Ann Rheum Dis* 2013.
- 14 Bathon JM, Martin RW, Fleischmann RM, *et al*. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *N Engl J Med* 2000;343:1586–93.
- 15 St Clair EW, van der Heijde DM, Smolen JS, *et al*. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. *Arthritis Rheum* 2004;50:3432–43.
- 16 Breedveld FC, Weisman MH, Kavanaugh AF, *et al*. The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum* 2006;54:26–37.
- 17 Emery P, Breedveld FC, Hall S, *et al*. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. *Lancet* 2008;372:375–82.
- 18 Emery P, Fleischmann R, van der Heijde D, *et al*. The effects of golimumab on radiographic progression in rheumatoid arthritis: results of randomized controlled studies of golimumab before methotrexate therapy and golimumab after methotrexate therapy. *Arthritis Rheum* 2011;63:1200–10.
- 19 Weinblatt ME, Fleischmann R, Huizinga TW, *et al*. Efficacy and safety of certolizumab pegol in a broad population of patients with active rheumatoid arthritis: results from the REALISTIC phase IIIb study. *Rheumatology (Oxford)* 2012;51:2204–14.
- 20 Velagapudi RB, Noertersheuser PA, Awni WM, *et al*. Effect of methotrexate (MTX) coadministration on the pharmacokinetics (PK) of adalimumab (HUMIRA, Abbott), following a single intravenous (iv) injection. *Arthritis Rheum* 2003;48:S141.
- 21 Arnett FC, Edworthy SM, Bloch DA, *et al*. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315–24.
- 22 Aletaha D, Neogi T, Silman AJ, *et al*. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum* 2010;62:2569–81.
- 23 Aletaha D, Smolen J, Ward MM. Measuring function in rheumatoid arthritis: identifying reversible and irreversible components. *Arthritis Rheum* 2006;54:2784–92.
- 24 Lindqvist E, Jonsson K, Saxne T, *et al*. Course of radiographic damage over 10 years in a cohort with early rheumatoid arthritis. *Ann Rheum Dis* 2003;62:611–16.
- 25 Lard LR, Visser H, Speyer I, *et al*. Early versus delayed treatment in patients with recent-onset rheumatoid arthritis: comparison of two cohorts who received different treatment strategies. *Am J Med* 2001;111:446–51.
- 26 Kremer JM. Safety, efficacy, and mortality in a long-term cohort of patients with rheumatoid arthritis taking methotrexate: followup after a mean of 13.3 years. *Arthritis Rheum* 1997;40:984–5.
- 27 Weinblatt ME, Kremer JM, Coblyn JS, *et al*. Pharmacokinetics, safety, and efficacy of combination treatment with methotrexate and leflunomide in patients with active rheumatoid arthritis. *Arthritis Rheum* 1999;42:1322–8.
- 28 Kremer JM, Lee JK. The safety and efficacy of the use of methotrexate in long-term therapy for rheumatoid arthritis. *Arthritis Rheum* 1986;29:822–31.
- 29 Kavanaugh A, Fleischmann RM, Emery P, *et al*. Clinical, functional and radiographic consequences of achieving stable low disease activity and remission with adalimumab plus methotrexate or methotrexate alone in early rheumatoid arthritis: 26-week results from the randomised, controlled OPTIMA study. *Ann Rheum Dis* 2013;72:64–71.
- 30 Detert J, Bastian H, Listing J, *et al*. Induction therapy with adalimumab plus methotrexate for 24 weeks followed by methotrexate monotherapy up to week 48 versus methotrexate therapy alone for DMARD-naive patients with early rheumatoid arthritis: HIT HARD, an investigator-initiated study. *Ann Rheum Dis* 2013;72:844–50.
- 31 Weisman MH, Moreland LW, Furst DE, *et al*. Efficacy, pharmacokinetic, and safety assessment of adalimumab, a fully human anti-tumor necrosis factor-alpha monoclonal antibody, in adults with rheumatoid arthritis receiving concomitant methotrexate: a pilot study. *Clin Ther* 2003;25:1700–21.
- 32 Velagapudi RB, Noertersheuser PA, Awni WM, *et al*. Effect of methotrexate (MTX) coadministration on the pharmacokinetics (PK) of adalimumab (HUMIRA, Abbott), following a single intravenous (iv) injection. *Arthritis Rheum* 2003;48:S141.
- 33 Schiff MH, Simon LS, Dave KJ, *et al*. Self-administered methotrexate using a medi-jet auto-injector improves bioavailability compared with oral methotrexate in adults with rheumatoid arthritis. *Ann Rheum Dis* 2013;72(Suppl 3):249–50.
- 34 Keystone EC, Kavanaugh AF, Sharp JT, *et al*. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. *Arthritis Rheum* 2004;50:1400–11.



## Supplementary Figures

Figure S1. Clinical efficacy following 26 weeks of open-label adalimumab in combination with different doses of MTX. Proportion of patients achieving ACR50 (A), and ACR90 (B). Statistically significant increasing trends in the proportion of patients achieving ACR50 and ACR90 were observed with increasing doses of MTX in combination with adalimumab at weeks 16, 20, and 26. ACR, American College of Rheumatology; ADA, adalimumab; MTX, methotrexate. Missing values were imputed using non-responder imputation. \* and \*\* denote statistical significance at the 0.05, and 0.01 levels, respectively.

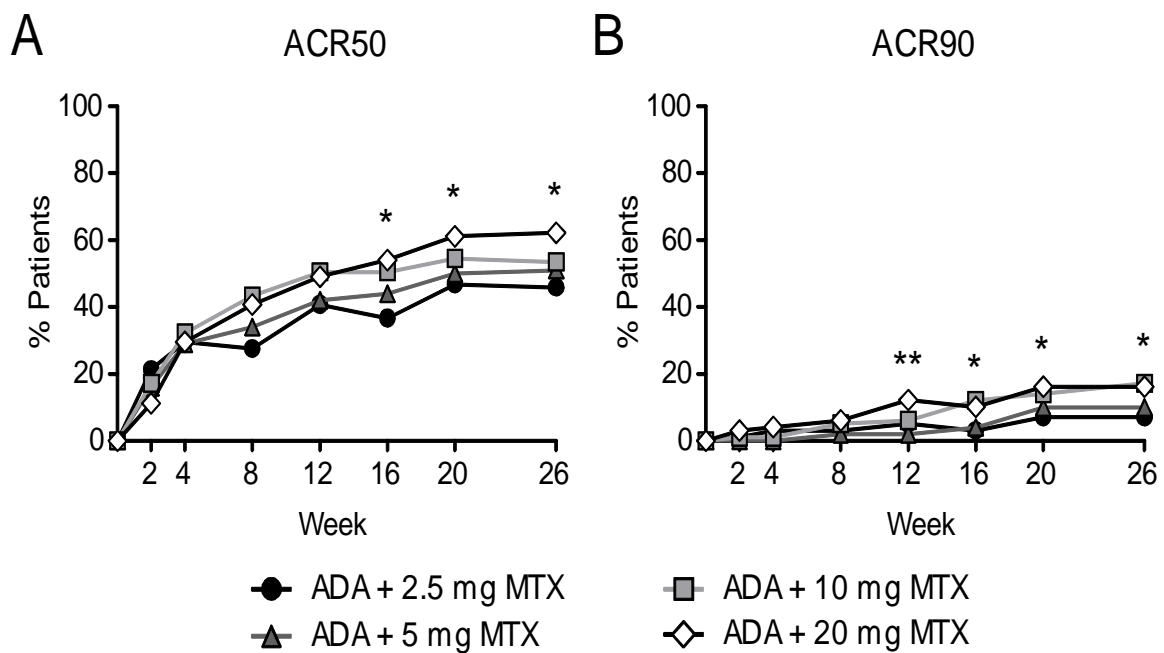
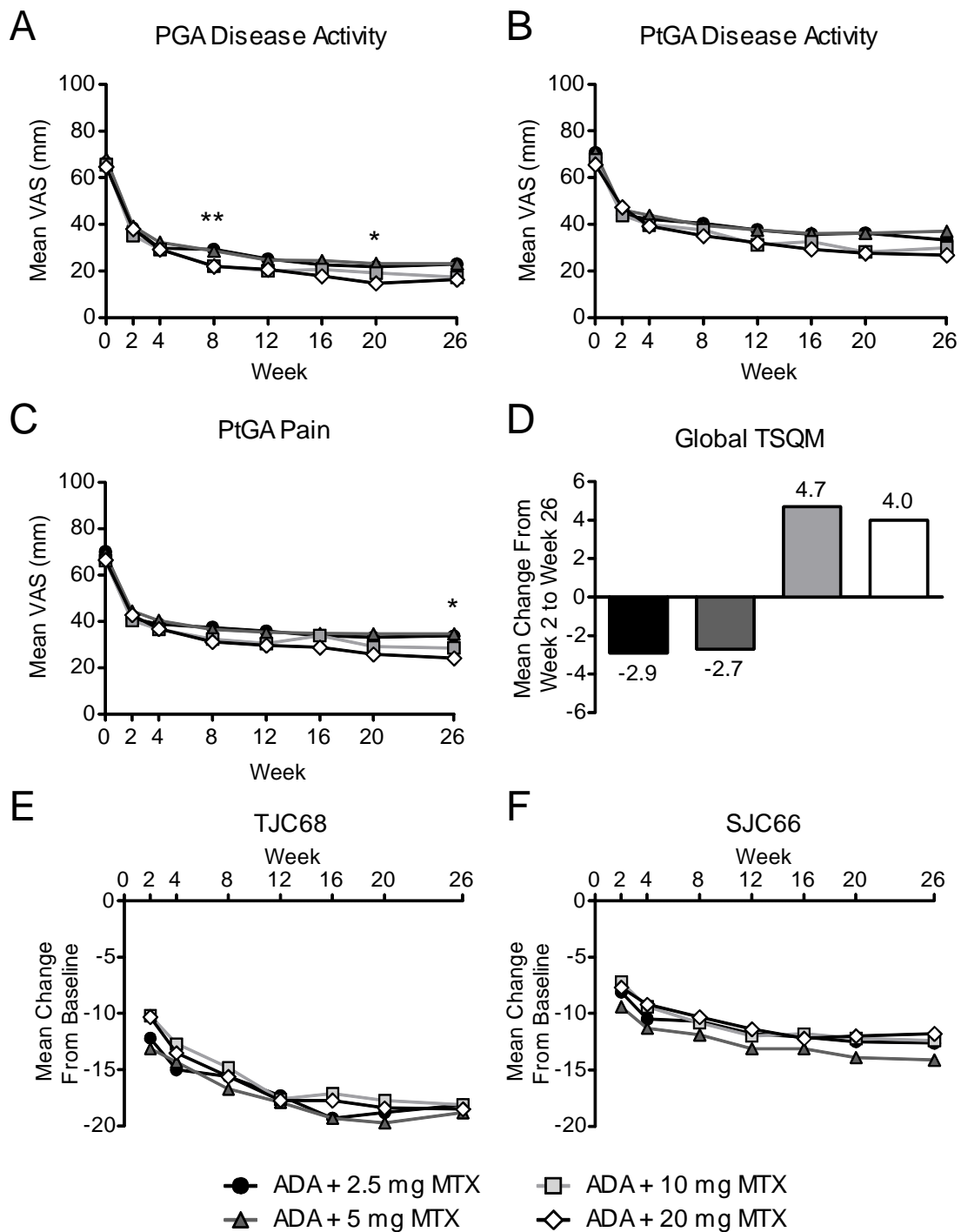


Figure S2. Clinical efficacy measured by PGA (A) and PtGA disease activity (B), PtGA pain (C), and change from baseline in TJC (D) and SJC (E). Only PtGA pain differences were statistically significant with increasing MTX dose in combination with adalimumab at week 26. PGA, physician’s global assessment; PtGA, patient’s global assessment; VAS, visual analogue scale; TSQM, Treatment Satisfaction Questionnaire for Medication; TJC68, tender joint count based on 68 joints assessed; SJC66, swollen joint count based on 66 joints assessed; ADA, adalimumab; MTX, methotrexate. Missing values were imputed using LOCF. \* and \*\* denote statistical significance at the 0.05 and 0.01 levels, respectively, using the Cochran-Armitage Trend test.



## Low-dose methotrexate may be the best starting option for patients initiating treatment with adalimumab

Some medicines used to treat inflammatory diseases such as rheumatoid arthritis may have different efficacy and safety depending on the dose used.

### INTRODUCTION

Rheumatoid arthritis is a chronic inflammatory disease that affects a person's joints, causing pain and disability. Methotrexate is commonly used in patients with rheumatoid arthritis, both on its own and in combination with a class of drugs called biologics. Despite having been used for many years in patients with rheumatoid arthritis, how methotrexate works against the disease is not exactly known. When used in combination with biologic drugs, it is thought that methotrexate can additionally help to prevent the development of antibodies to the biologic, which the body's immune system sometimes recognises as a foreign protein, and can therefore help to maintain efficacy. The dose of methotrexate used can vary widely, from 7.5 mg to 25 mg a week.

### WHAT DID THE AUTHORS HOPE TO FIND?

The authors wanted to see whether the dose of methotrexate used in combination with a biologic drug called adalimumab has an impact on the overall efficacy and safety in patients with early rheumatoid arthritis, and if it was possible to identify an optimum dose that should be used.

### WHO WAS STUDIED?

The study included 395 patients diagnosed with early rheumatoid arthritis. All patients were over the age of 18, had suffered from severe rheumatoid arthritis for less than 1 year, and had not previously received methotrexate or a biologic drug, or more than one other type of disease-modifying anti-rheumatic drug (usually called DMARDs).

### HOW WAS THE STUDY CONDUCTED?

This was a randomised, double-blind trial, which means that patients were assigned by chance to one of four treatment groups to receive one of four different doses of methotrexate in combination with a biologic drug called adalimumab and folic acid. Using chance in this way means that the groups will be similar and will allow the treatment under investigation (different doses of methotrexate) to be compared objectively. During the treatment neither patients nor their doctors knew which group they were in.

A series of assessments were performed at baseline and over the next 26 weeks. These recorded clinical and functional status, including functional ability, whether there was any progression or joint damage, and patient quality of life. Safety issues were also recorded. Blood samples were also taken to work out whether patients developed antibodies to adalimumab – a phenomenon which can affect the efficacy of biologic drugs.

### WHAT WERE THE MAIN FINDINGS OF THE STUDY?

The study found that more patients saw an improvement in their rheumatoid arthritis disease score with increasing doses of methotrexate, and were more likely to achieve remission. There were fewer antibodies to adalimumab with increasing doses of methotrexate. No difference in progression of joint damage was seen between the different groups, suggesting that methotrexate dose may not affect this. The study also found that patients experienced more side effects with increasing methotrexate dose; people were more likely to have an infection while taking a high dose of methotrexate, but these were not serious.

The authors concluded that higher doses of methotrexate may be more likely to result in better clinical outcomes, although not in joint progression. For patients with early RA starting adalimumab combination therapy, it may be possible to achieve clinical results with a lower initial dose of methotrexate than had previously been thought – perhaps as low as 10 mg a week.

### ARE THESE FINDINGS NEW?

Yes – this is the first blinded, controlled clinical trial that has tried to find out the lowest effective dose of methotrexate in combination with biologic therapy in patients with early, active rheumatoid arthritis of the type often seen in clinical practice. Determining the best methotrexate starting dose in these patients provides an important insight into the optimal management of these patients for doctors in clinical practice.

### HOW RELIABLE ARE THE FINDINGS?

There are some limitations which may affect how reliable the findings are. The study looked at different doses of methotrexate in patients with early and aggressive disease who had not received a biologic drug before, and these results may not apply to patients who have received many other drugs previously, or who have had their disease for longer. Also, some of the results seen may be specific to adalimumab, and methotrexate might not behave in exactly the same way in combination with other biologic drugs.

Patients receiving the highest dose in the study (20 mg) actually started at 10 mg a week and had their dose gradually increased over 8 weeks to try to help prevent side effects, which means that the results for these patients include some time at a lower dose. The authors also acknowledged that not investigating doses higher than 20 mg may affect how useful these results are, as doses greater than this are often used in clinical practice.

### WHAT DO THE AUTHORS PLAN ON DOING WITH THIS INFORMATION?

This information will be used to support doctors in choosing lower doses of methotrexate for their patients. Further studies may be undertaken to see if the same results can be repeated with other biologic drugs or in different groups of patients.

### WHAT DOES THIS MEAN FOR ME?

Patients with rheumatoid arthritis who are taking a biologic drug will often receive methotrexate as well because it is thought that it can help to achieve better results than when biologics are used on their own, but it may also increase the number of side effects seen. These results might mean that doctors try lower doses of methotrexate to start with. Patients who are concerned should speak to their doctor.

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