EXTENDED REPORT

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

Gerd-Rűdiger Burmester,[1] Alan J Kivitz,[2] Hartmut Kupper,[3] Udayasankar Arulmani,[4] Stefan Florentinus,[5] Sandra L Goss,[4] Suchitrita S Rathmann,[4] Roy M Fleischmann[6]

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-naive 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)[1] and the American College of Rheumatology (ACR)[2] as it has been shown to be efficacious, with an acceptable toxicity profile, and is cost effective.[3] [4] 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.[4] [5]

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.[6] 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.[7] [8] Older literature has suggested that MTX toxicity is dose-dependent and low dose MTX monotherapy treatment can be effective.[9–13] 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.[1] [2] 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).[14–19]

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.[20] Optimising adalimumab combination therapy to achieve disease control should identify the minimal

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 ≥18 years of age with RA defined by either the 1987 revised ACR classification[21] or the new ACR/EULAR diagnostic criteria.[22] Patients must have had a disease duration <1 year, 28-joint count disease activity score (DAS28) based on C reactive protein (CRP)≥3.2, swollen joint count (SJC)≥6 of 66 joints assessed, tender joint count (TJC)≥8 of 68 joints assessed, CRP≥1.5 mg/dL or erythrocyte sedimentation rate ≥28 mm/h, and ≥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 (≤10 and 2.8, respectively); simplified disease activity index (SDAI) LDA and remission (≤11 and 3.3, respectively); minimal clinically important differences in function (Health Assessment Questionnaire Disability Index (HAQ-DI) change≤−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 (ΔmTSS ≤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, ΔmTSS ≤0.5 and DAS28(CRP) <3.2 (CDC_{LDA}) or <2.6 (CDC_{REM}), 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±0.97, HAQ-DI of 1.57±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 4 weeks. Clinical LDA and remission, assessed 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.
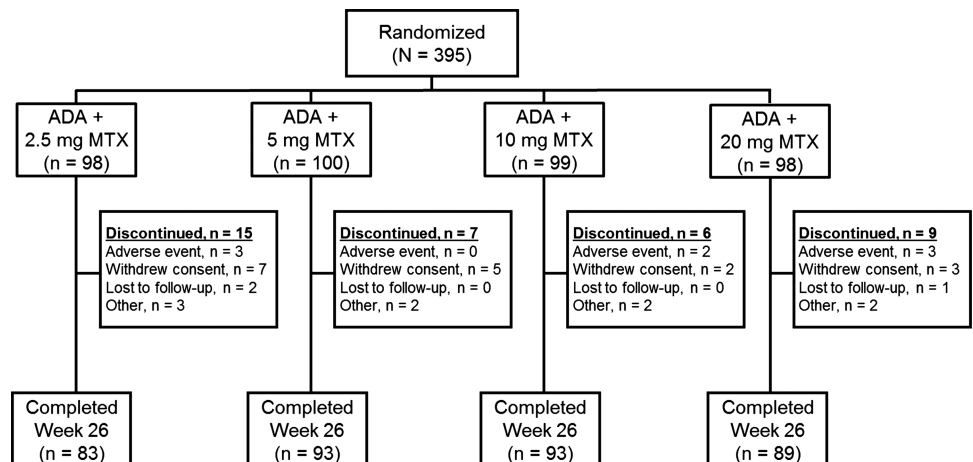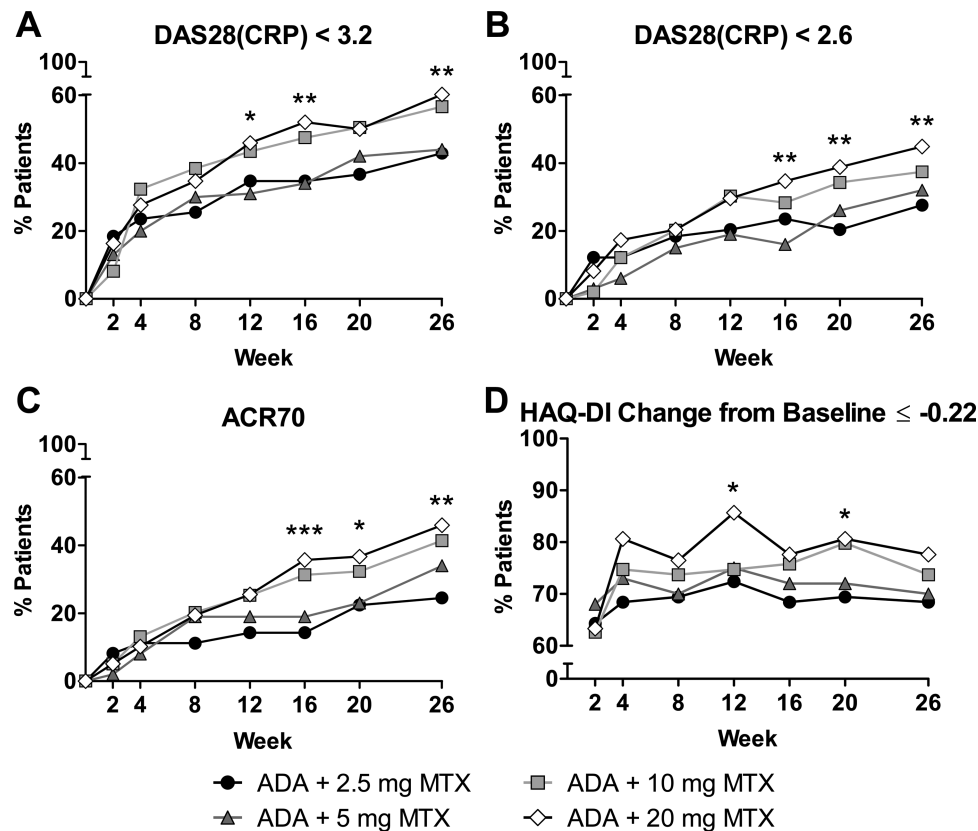
Figure 2 Clinical and functional efficacy following 26 weeks of open-label adalimumab in combination with different doses of MTX. Proportion of patients achieving DAS28(CRP) <3.2 (A), <2.6 (B), ACR70 (C) and change from baseline HAQ-DI≤−0.22 (D). DAS28, 28-joint disease activity score; CRP, C reactive 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≤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 (±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 ~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 V.1.4, 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 ΔmTSS 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_{LDA} and CDC_{REM} 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_{LDA} compared with ~20% of patients in the lower MTX groups; similarly, 26.5% of patients achieved
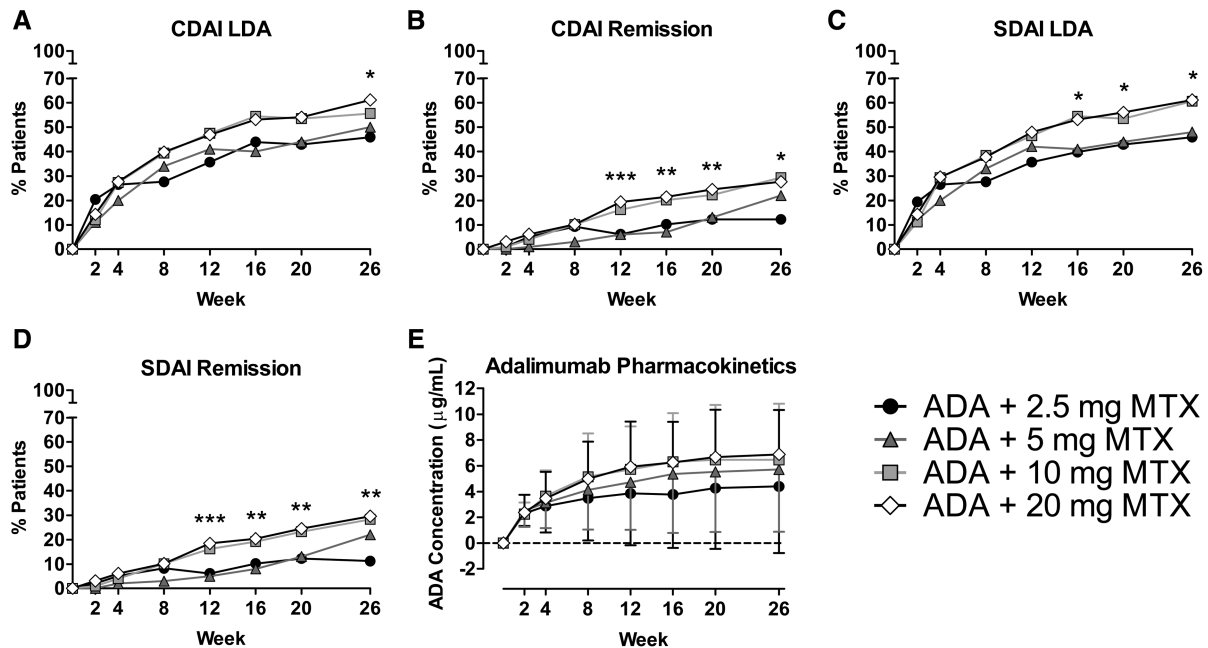
Figure 3 Clinical LDA, remission and adalimumab pharmacokinetics following 26-week treatment with adalimumab in combination with ascending MTX doses. Proportion of patients achieving LDA or remission measured by CDAI (A and B, respectively) or SDAI (C and D, respectively). Mean adalimumab trough concentrations (±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$_{REM}$ 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 (ΔmTSS ≤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.
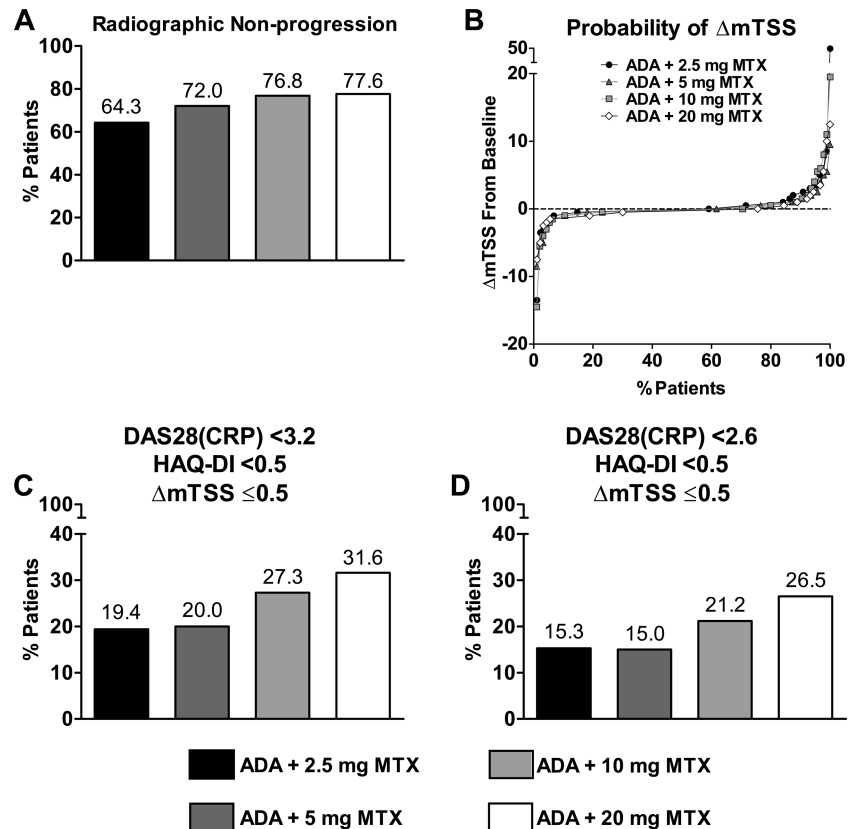
Table 2 Safety results following 26-week treatment, n (%)

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 (× 10⁹/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 (× 10⁹/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[23][24] 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[25] 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;[26–28] 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.[1][2] 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.[16][29][30]

Low adalimumab serum concentrations have previously been shown to decrease treatment efficacy;[31] examining different controlled doses of MTX with a constant adalimumab dose has not be 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.[20][32] 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,[33] 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.[31][34] 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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