Are switches from oral to subcutaneous methotrexate or addition of ciclosporin to methotrexate useful steps in a tight control treatment strategy for rheumatoid arthritis? A post hoc analysis of the CAMERA study

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Are switches from oral to subcutaneous methotrexate or addition of ciclosporin to methotrexate useful steps in a tight control treatment strategy for rheumatoid arthritis? A post hoc analysis of the CAMERA study

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ABSTRACT

Objective To investigate the effects of a switch from oral methotrexate (MTX) to subcutaneous MTX (scMTX) or adding ciclosporin to oral MTX with a simultaneous reduction of the MTX dose, in case of adverse events (AE) or insufficient effect (IE) in rheumatoid arthritis (RA).

Methods The tight control treatment arm of the Computer Assisted Management in Early RA (CAMERA) trial was evaluated. The change in 28-joint Disease Activity Score (DAS28) after taking scMTX (over 1 month) or adding ciclosporin (over 3 months) was compared to the average monthly change in the preceding 3 months. Analyses were performed separately for strategy steps because of AE or IE.

Results Of 151 patients, 57 needed the scMTX strategy step (21 because of AE, 36 because of IE) and 40 the following ciclosporin strategy step (20 and 20, respectively). The decrease in DAS28 after taking the scMTX strategy step was 0.30 points ($p<0.05$); no significant change in DAS28 was seen after the ciclosporin strategy step. In both strategy steps for AE or IE, quite similar observations were made. Of the patients who took the scMTX strategy step, 63% showed improvement.

Conclusion scMTX seems a useful treatment step after oral MTX in a tight control strategy, whereas the ciclosporin step seems ineffective.

INTRODUCTION

One of the studies demonstrating benefits of early tight control treatment of rheumatoid arthritis (RA) is the Computer Assisted Management in Early RA (CAMERA) trial, showing better 2-year clinical effects of an intensive (tight control) strategy compared to a conventional strategy.[1] In this trial, patients were treated with methotrexate (MTX) in stepwise increasing dosages. In case of insufficient efficacy (IE) at the maximum oral dose of MTX (30 mg/week) or in case of adverse events (AE), the next strategy step was a switch to the same dose subcutaneously (scMTX) and the step thereafter was addition of ciclosporin with a reduction of MTX to a maximum of 15 mg/week. Although the intensive strategy was more effective than the conventional strategy, the efficacy of the strategy steps described above is not clear. The aim of the present evaluation was to analyse the efficacy of these strategy steps within the CAMERA trial.

PATIENTS AND METHODS

Patients of the tight control arm of a 2-year randomised, open-label prospective multicentre treatment strategy trial (CAMERA) were evaluated.[1] At study entry all patients fulfilled the 1987 revised American College of Rheumatology (ACR) criteria for RA, had a disease duration of less than 1 year, and were disease-modifying antirheumatic drug and glucocorticoid naïve. The medical ethics committees of all participating hospitals approved this trial, and all patients gave written informed consent before entering.

Patients were given 7.5 mg/week oral MTX and the dose was increased stepwise by 5 mg/week until remission, the maximum dose of 30 mg/week or the maximum tolerable dose was reached. Stepwise increase of the therapy was dependent on predefined criteria and strategy steps could be taken at monthly intervals. Predefined criteria of response were calculated by a computer decision program and determined as >20% improvement in swollen joint count (SJC) and improvement in two of three of the following variables: tender joint count (TJC), erythrocyte sedimentation rate (ESR) and visual analogue scale (VAS) for well-being, compared to previous visit. The criteria for remission were defined as SJC=0 and two out of the following criteria: TJC≤5, ESR≤20 mm/h and VAS≤20 mm. Sustained remission was defined as remission during four subsequent visits.[1]

If at the maximum (tolerable) dose of MTX there was no remission, this dose was administered subcutaneously (scMTX). If the predefined goal of remission at the subsequent visit was not met, ciclosporin (starting dose 2.5 mg/kg/day; increased stepwise by 0.5 mg/kg/day monthly until maximum dose of 4.0 mg/kg/day) was added to the MTX therapy, which was then decreased to 15 mg/week orally because of the negative effect of ciclosporin on kidney function, possibly increasing MTX toxicity. In case of serious AE on oral MTX (eg, pneumonitis), the scMTX step was skipped.

Statistical analyses

The change in DAS28 of the scMTX strategy step was evaluated after 1 month and that of the ciclosporin strategy step, with increasing dosages and a more delayed response, after 3 months. These changes were compared with the average monthly change in DAS28 in the preceding 3 months before the respective steps and tested with paired sample t tests for patients who took the steps because of AE or IE of treatment, separately.

To evaluate if there was a trend in the course of the DAS28, general linear model (GLM) repeated measures were performed over 4 months for the scMTX strategy step and over 6 months for the ciclosporin strategy step.

The number of patients responding to each of these steps was defined by the difference between the individual mean monthly DAS28 change in the 3 months preceding the treatment strategy step and the DAS28 change at 1 month (scMTX strategy step) or at 3 months (ciclosporin strategy step). The patient was considered responding if this difference was ≤0, indicating at least an equal decline in the DAS28 after compared to before taking the step.

The statistical software SPSS V.15.0 (SPSS, Chicago, Illinois, USA) was used for analyses; a p value <0.05 was considered to be statistically significant.

RESULTS

Of the 151 patients in the tight control strategy, 57 needed the scMTX strategy step (21 because of AE and 36 because of IE) and 40 the ciclosporin strategy step (20 and 20, respectively). Of those who took the ciclosporin strategy step because of AE of MTX, seven did not take the scMTX strategy step first and two patients stopped MTX treatment because of serious AE.

Patient characteristics of the patients taking the scMTX and ciclosporin strategy steps (at the moment of taking the steps) are shown in table 1. Patients who took the scMTX strategy step because of AE did this on average after 14 visits (50±27 weeks; mean±SD) and had had a mean dose of 25 mg/week (SD 6.5) of (oral) MTX. This was on average after 11 visits (38±14 weeks) for IE with the maximum dose of 30 mg/week according to the strategy. For the ciclosporin strategy step this was after 16 visits (58±27 weeks) with a mean dose of 26 mg/week (SD 7.9) MTX because of AE and 14 visits (50±13 weeks) with 30 mg/week for IE, according to the strategy.

Changes in DAS28

The mean decrease in the DAS28 1 month after taking the scMTX strategy step was 0.30 points (p<0.05); 0.21 points more (NS) than before taking the step. Quite similar results were seen for AE and IE (figure 1A). In contrast, the change in the DAS28 3 months after taking the ciclosporin strategy step was 0.01 points increase in DAS28 (NS); which was 0.06 points worse compared to before taking the step (NS). The results were similar for the strategy steps because of AE and IE (figure 1B).

The course of the DAS28

For patients of the scMTX strategy step there was a decrease in the course of the DAS28 of 0.5 points over the 4-month evaluation period (p<0.01; figure 1A), similar for AE (0.4 points; NS) and IE (0.6 points; p<0.001) groups. For the ciclosporin strategy step, there was no trend in the DAS28 over the 6-month evaluation period (p=0.37; figure 1B), similar for AE and IE groups (both NS).

Numbers of patients responding to each strategy step

Following the switch to scMTX, 36 patients (63%, 95% CI 50% to 70%) responded (ie, had an equal or better course in DAS28 compared to the preceding months), but 21 did not (figure 2A); 6 of these 21 improved but less than the improvement in DAS28 present before the switch. In the ciclosporin group 19 patients (48%, 95% CI 32% to 64%) responded, whereas 21 did not (figure 2B); in 20 of these 21 patients the DAS28 increased. The response rates were 57% and 67% for patients who took the scMTX strategy step because of AE or IE, and 35% and 60%, respectively for patients taking the ciclosporin strategy step.

DISCUSSION

The results suggest that the scMTX strategy step after oral MTX was useful regarding a further decrease in disease activity,

Table 1 Characteristics of patients who took the subcutaneous methotrexate (scMTX) strategy step or the (next) ciclosporin strategy step

	scMTX strategy step			Ciclosporin strategy step		
Characteristic	**Total (n=57)**	**AE (n=21)**	**IE (n=36)**	**Total (n=40)**	**AE (n=20)**	**IE (n=20)**
Female gender, %*	44 (77)	17 (81)	27 (75)	30 (75)	16 (80)	14 (70)
Age, years*	54 (16)	53 (13)	54 (17)	52 (14)	51 (11)	53 (16)
Weight, kg*	65 (26)	69 (19)	62 (29)	64 (30)	66 (26)	62 (35)
ESR, mm/first hour	23 (15)	28 (19)	20 (11)	24 (19)	27 (24)	21 (12)
CRP, mg/litre	12 (21)	17 (31)	10 (13)	12 (16)	12 (12)	13 (20)
RF^+, %*	31 (54)	13 (62)	18 (50)	23 (58)	14 (70)	9 (45)
Morning stiffness, min	32 (49)	50 (65)	22 (32)	29 (34)	34 (35)	24 (33)
VAS general, mm	29 (26)	35 (31)	25 (22)	30 (25)	33 (27)	27 (23)
VAS pain, mm	23 (24)	27 (27)	21 (22)	23 (20)	25 (23)	21 (18)
TJC	4 (6)	5 (6)	4 (5)	4 (5)	3 (4)	5 (6)
SJC	4 (5)	5 (6)	4 (4)	3 (4)	3 (3)	4 (5)
DAS28	3.9 (1.3)	4.2 (1.7)	3.8 (1.0)	3.8 (1.1)	3.7 (1.2)	3.8 (1.0)
SHS	1.6 (4.6)	0.7 (1.2)	2.1 (5.7)	4.2 (9.5)	4.1 (8.9)	4.3 (10.2)
MTX dose, mg/week	28 (4)	25 (7)	30 (0)	28 (6)	26 (8)	30 (0)
Time until step (no. visits)	12 (5)	14 (7)	11 (4)	15 (5)	16 (7)	14 (3)

Data represent the moment the strategy step was taken (except for age, gender, weight and RF, which are baseline data indicated by asterisks). Data show mean (SD) for continuous variables and number of patients (%) for categorical data. MTX dose refers to dose (oral or subcutaneous) of MTX when patients took the strategy step; time until step refers to the number of visits compared to baseline (start of study) after patients took the strategy step; total refers to the total group of patients taking the strategy step.
AE, adverse events; CRP, C reactive protein (0–150 mg/litre); DAS28, 28-joint Disease Activity Score; ESR, erythrocyte sedimentation rate (2–140 mm/first hour); IE, insufficient effect; RF^+, rheumatoid factor positive, morning stiffness (0–180 min); SHS, Sharp/van der Heijde score; SJC, swollen joint count (0–26); TJC, tender joint count (0–26); VAS, visual analogue scale (0–100 mm).

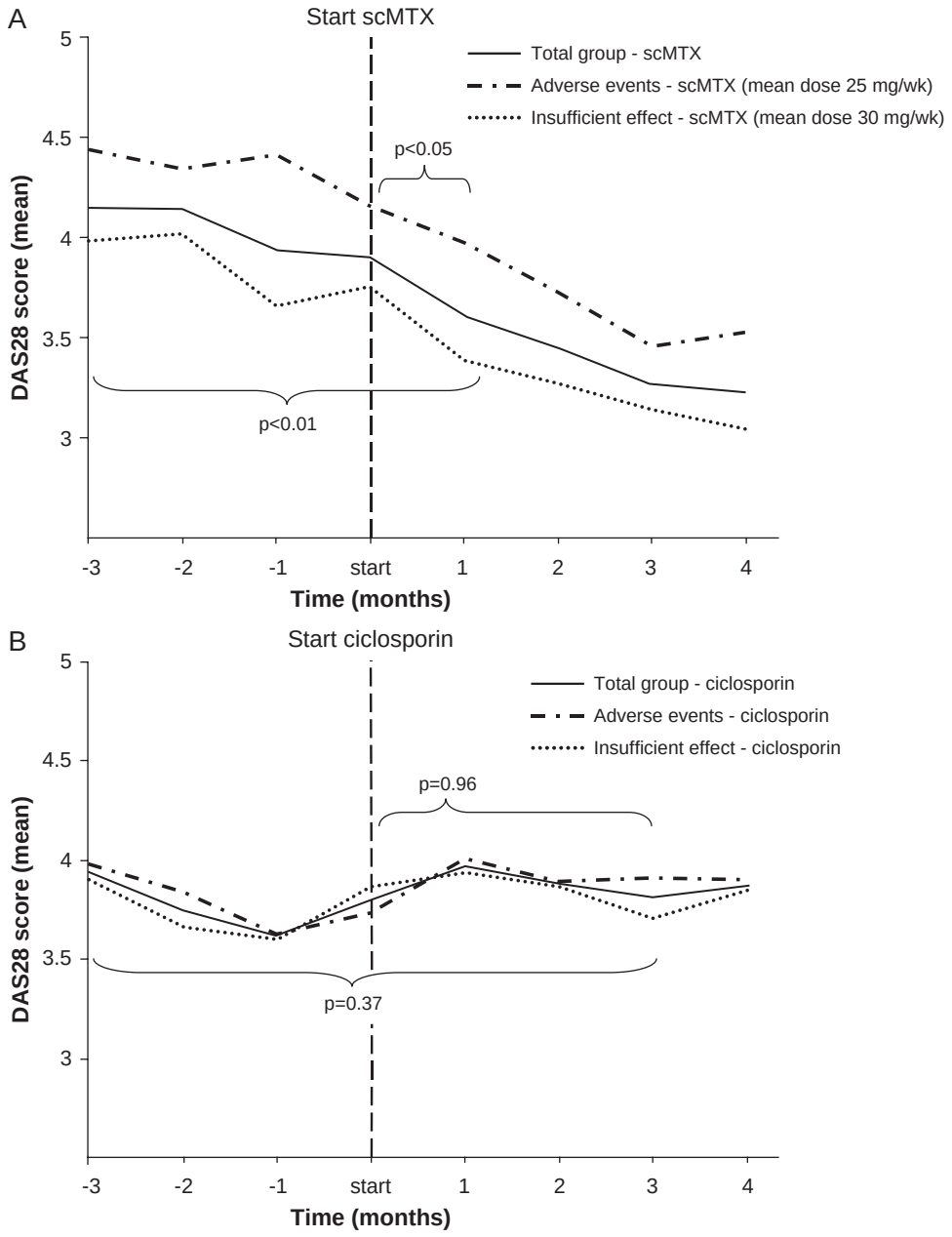

Figure 1 The course of the 28-joint Disease Activity Score (DAS28) for patients who took the subcutaneous methotrexate (scMTX) strategy step (A) or the ciclosporin strategy step (B). The solid lines show the course of the DAS28 for the total groups of patients taking scMTX or ciclosporin strategy steps, the dashed lines show the course of the DAS28 for patients taking the strategy steps because of adverse events (AE) and the dotted lines for patients taking the strategy steps because of insufficient effect (IE). The p values shown are for the total groups of patients taking scMTX or ciclosporin strategy steps.

specifically for those in the IE subgroup. In contrast, the following ciclosporin strategy step seems less useful within the tight control strategy.

Limitations of this study are that the trial had not been designed to investigate the efficacy of steps within the treatment strategy. No control group of patients not taking the strategy step was available to compare the results to. Our analyses were based on the change in the course of the disease activity after taking each step compared with the average monthly change in the disease activity course before taking the step. Of other intensive treatment strategy studies such as Tight Control of RA (TICORA), Behandel Strategieën (BeST), Combinatietherapie bij Reumatoïde Arthritis (COBRA) and Ciclosporin, Methotrexate, Steroid in RA (CIMESTRA)[2–6] the effectiveness of individual strategy steps is not well known. Therefore analyses such as these, although suboptimal, are useful to determinate optimal tight control strategies from the different approaches used.

One reason scMTX is a successful strategy step could be the higher bioavailability compared to oral MTX.[7 8] Another randomised controlled trial with MTX-naïve patients with early RA showed that starting with scMTX was more efficient than starting with oral MTX treatment at a dosage of 15 mg/week; respectively 78% and 70% of patients achieved an ACR20 response after 24 weeks.[9] In another study more than 70% of patients with juvenile idiopathic arthritis failing on oral MTX because of IE or AE met criteria for improvement ($p<0.05$) after switch to scMTX, without increased toxicity.[10]

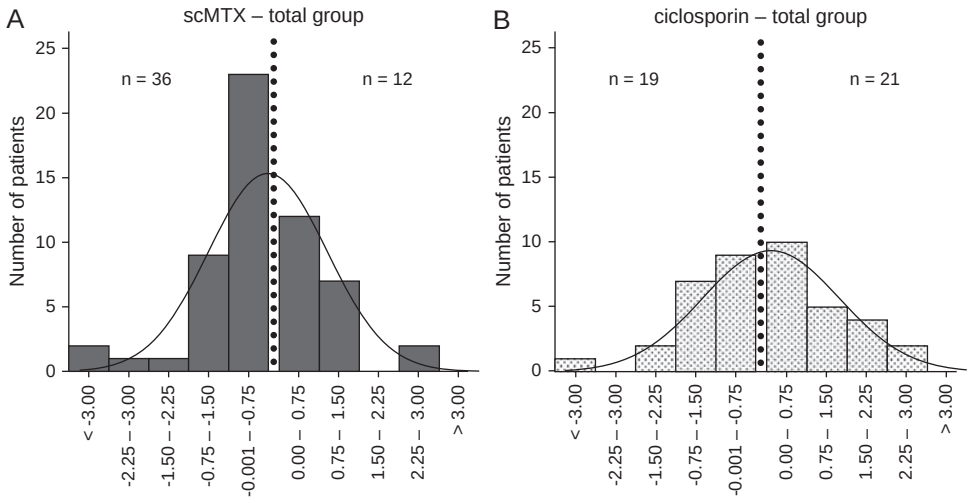

Figure 2 The individual responses are presented as categorised changes, based on the differences between the individual mean monthly 28-joint Disease Activity Score (DAS28) change in the 3 months before taking the treatment strategy step minus the DAS28 change after 1 month (subcutaneous methotrexate (scMTX) strategy step; (A)) or 3 months (ciclosporin strategy step; (B)) after taking the steps. Positive values denote an increase (deterioration) and negative values a decrease (improvement) in the DAS28 course after taking the strategy step as compared to the mean monthly change in DAS28 in the 3 months before taking the strategy step Left of dotted vertical line, deterioration; right of dotted line, improvement.

The patients who needed the ciclosporin step already had failed on the (sc)MTX treatment and besides had worse radiographic outcome; they could represent a subset more refractory to medication and might be good candidates for a biological in an earlier phase of their treatment. Additionally, the reduction of the MTX dose when taking the ciclosporin step could be a reason for the lack of effect. In (nearly) untreated patients with RA combination therapy of MTX and ciclosporin led to a better clinical response when compared to MTX or ciclosporin alone.[5 11 12] However, in our study patients starting ciclosporin had experienced an insufficient response on MTX. In another study[13] ciclosporin or placebo was added to MTX in patients with (long standing) severe RA treated with MTX with a maximum dose of 15 mg/week and a partial response to treatment. At 6 months later, 48% of patients in the MTX/ciclosporin group met the ACR20 criteria compared to 16% of the MTX/placebo group. This study differs from the CAMERA trial regarding the tight control principle, disease duration and starting point of combination treatment (partial response on 15 mg/week MTX versus no remission on maximally 30 mg/week MTX).

In conclusion, the scMTX strategy step seems an effective step after oral MTX in a tight control strategy in early RA, especially when taken because of IE, whereas ciclosporin (as a following step after the scMTX step) cannot be recommended.

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Patient consent Obtained.

Ethics approval This study was conducted with the approval of the METC UMC Utrecht, The Netherlands.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

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