The CAMERA (Computer-Assisted Management in Early Rheumatoid Arthritis) studies

J.W.G. Jacobs
on behalf of the Utrecht Rheumatoid Arthritis Cohort study group

Department of Rheumatology and Clinical Immunology, University Medical Center Utrecht, The Netherlands.

Johannes W.G. Jacobs, MD, PhD

Please address correspondence to: Johannes W.G. Jacobs, MD, PhD, Department of Rheumatology and Clinical Immunology, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands.
E-mail: j.w.g.jacobs@umcutrecht.nl

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ABSTRACT

The history, main issues and results of the two tight control CAMERA (Computer-Assisted Management in Early Rheumatoid Arthritis) studies are described. The first CAMERA study showed favourable and superior effects of a tight control methotrexate-based strategy, compared to that of a conventional methotrexate-based strategy. In CAMERA-II, the results were even better when adding 10 mg prednisone daily for 2 years to the methotrexate-based, tight control strategy. In all, the CAMERA studies have shown good results in the treatment of early RA patients with conventional anchor drugs, aiming for remission, making use of a feasible and simple computer decision program.

Introduction and history

The two CAMERA (Computer-Assisted Management in Early Rheumatoid Arthritis) clinical trials were research activities of the Utrecht Rheumatoid Arthritis Cohort study group. This involves a Dutch ongoing collaboration between the University Medical Center Utrecht and surrounding non-university hospitals, which started in 1989 as the Rheumatic Research Foundation Utrecht (SRU). The first investigations of the SRU indicated that treatment with disease-modifying anti-rheumatic drugs (DMARDs) should be initiated immediately after diagnosis of rheumatoid arthritis (RA), instead of applying the traditional pyramid model, beginning with non-steroidal anti-inflammatory drugs (NSAIDs) only (1). Thereafter, we showed that methotrexate (MTX) is the most effective conventional DMARD with the least toxicity (2), in line with results of other research groups.

Based on these observations, we applied MTX as anchor drug in the first CAMERA study (3), one of the earliest treat-to-target studies, aiming for remission. Its research question was whether an MTX-based tight control strategy would yield better results than the conventional MTX-based strategy at that time. In this study more patients with early RA in the tight control MTX strategy group compared to the conventional MTX strategy group achieved at least one period of remission. Results of another Utrecht study documented that glucocorticoids have disease modifying properties in early RA (4), again in agreement with other studies. The observations of these two clinical trials led to the second CAMERA study (CAMERA-II), with the main research question of whether prednisone would still have disease modifying and symptom controlling properties in early RA, when a tight control MTX-based strategy was applied (5).

This article summarises the main issues and results of the two tight control CAMERA studies.

The first CAMERA study

This was a two-year randomised, open-label prospective multicentre treatment strategy trial (3). Patients had been included in this study between 1999 and 2003. At study entry all 299 patients fulfilled the 1987 revised American College of Rheumatology (ACR) criteria for RA (6), had a symptom duration of less than 1 year, and were DMARD- and glucocorticoid-naïve. Patients were randomised to either a tight control MTX-based treatment strategy (n=151), based on computer guided monthly assessments of predefined response criteria, or to a conventional MTX-based strategy (n=148), based on regular clinical practice with three-monthly visits. Both strategies were aiming at remission.

For both strategies, data on swollen joint count (SJC), tender joint count (TJC), both assessing 38 joints, erythrocyte sedimentation rate (ESR), and

visual analogue scale (VAS) for global health were collected by the rheumatologist at every visit. In the tight control strategy these data were entered at each monthly visit into a computer decision program by the rheumatologist. The program calculated whether or not there was a >20% improvement (defined as >20% improvement in SJC and in ≥ two out of TJC, ESR, and VAS), compared to previous visit one month earlier and whether or not there was remission (defined as SJC=0 and ≥ two out of this three criteria: TJC ≤3, VAS ≤20 mm, ESR ≤20 mm/h[1st]) (Fig. 1). If neither a >20% improvement or remission was present, the strategy was intensified according to protocol. For the conventional strategy, dose adjustments were performed based on the opinion of the treating rheumatologist (mainly focused on the SJC) at each 3-monthly visit.

Both strategies started with oral MTX 7.5 mg/wk, which could be stepped up in steps of 5 mg/w towards a maximum oral MTX dose of 30 mg/wk. This was followed, if needed, by switching from oral to subcutaneous MTX (scMTX) and, as next step, by adding cyclosporine to the MTX medication.

If patients fulfilled the criteria for sustained remission, defined as remission for at least three months, MTX was reduced stepwise by 2.5 mg/week as long as patients met the remission criteria; otherwise the dose of MTX was continued or increased again according to protocol. At baseline and subsequently yearly, joint damage was assessed on radiographs of hands and feet.

Seventy-six (50%) patients in the tight control strategy group achieved at least one period of sustained remission during the two year trial (the primary outcome), *versus* 55 patients (37%) in the conventional strategy group (p=0.03). Areas under the curve for nearly all clinical disease activity variables were significantly lower – that is, there was a better clinical effect – for the tight control strategy group compared with the conventional strategy group. In both strategy groups, approximately 50% of patients did not progress regarding radiological joint damage over the two years. For the other 50%, there was a trend toward less progression in the tight control strategy group, compared to the conventional strategy group.

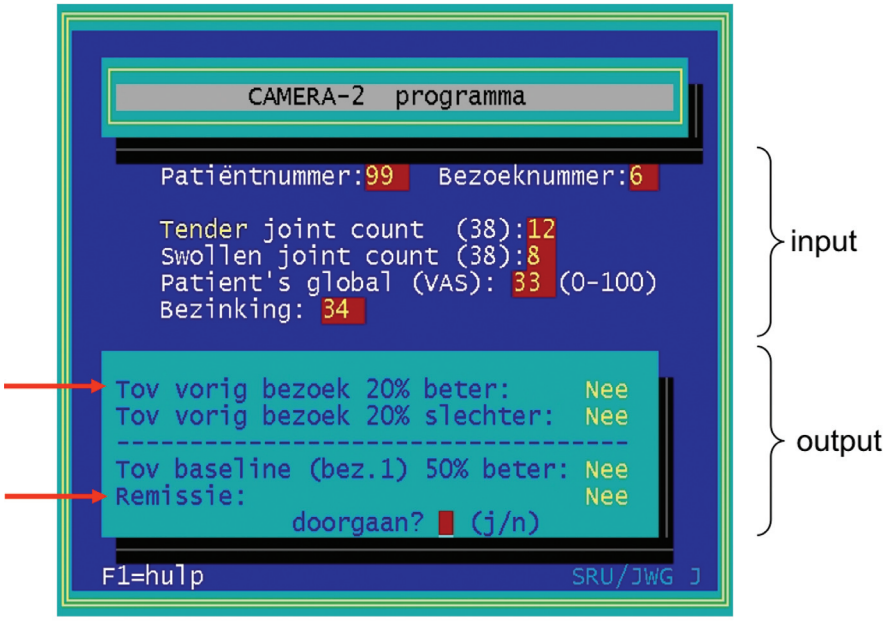


Fig. 1. The CAMERA studies computer decision program.
In the input section, patient number ("Patiëntnummer"), visit number ("Bezoeknummer"), tender joint count assessing 38 joints (TJC), swollen joint count assessing 38 joints (SJC), patient's global visual analogue scale (VAS) and erythrocyte sedimentation rate (ESR, "Bezinking") are imputed.
In the output section, at the arrows, the result regarding > 20% improvement compared to previous visit one month earlier ("Tov vorig bezoek 20% beter") is given as yes ("ja") or no ("nee"), and whether there is remission ("Remissie") yes ("ja") or no ("nee").
>20% improvement was defined as >20% improvement in SJC AND (Boolean) >20% improvement in ≥ two out of this three: TJC, ESR, and VAS.
Remission was defined as SJC=0 AND (Boolean) ≥ two out of this three criteria: TJC ≤3, VAS ≤20 mm, ESR ≤20 mm/h[1st]. On these results, protocolised strategy steps were based. Programmer: JWG J.

We concluded that tight control treatment with MTX, aiming for remission, resulted in a better outcome over two years and that the computerised decision program could be a helpful tool in daily clinical practice.

In an analysis of adverse events (7), we found that more patients in the tight control strategy group than in the conventional strategy group had experienced MTX-related adverse-effects, but that most adverse effects were relatively mild. MTX-related adverse-effects were associated with a higher body mass index, diminished creatinine clearance and increased serum liver enzymes at baseline. Furthermore we showed that switching from oral to scMTX had been a useful strategy step in the tight control strategy of the first CAMERA study, whereas the cyclosporine strategy step had been ineffective (8). Good response to treatment at 6 months in the first CAMERA trial predicted significantly better 5-year clinical and radiographic outcomes (9), corroborating the "window-of-opportunity" hypothesis.

The second CAMERA study (CAMERA-II)

In this 2-year, prospective, randomised, placebo-controlled, double-blind, multicentre trial, all 236 patients with early RA (symptoms <1 year) were treated with an MTX-based tight control strategy and were randomly assigned to prednisone 10 mg per day or placebo-prednisone (5). The research questions were whether prednisone would still have symptom controlling and disease modifying properties in early RA (4), when a tight control MTX-based strategy is applied, and whether the clinical results of the first CAMERA study could be improved with prednisone.

MTX treatment was in both groups tailored to the individual patient at monthly visits on the basis of predefined response criteria aiming for remission, applying the same variables and the same computer decision program as used in

the first CAMERA study (Fig. 1). The MTX step-up strategy was identical to that of the first CAMERA study, except for the starting dose of 10 mg MTX per week. Shortly after the trial was started, the protocol was amended: adalimumab replaced cyclosporine as a last strategy step, to be added to the maximum dosage of scMTX (Fig. 2). This amendment was based on our finding of lack of effect of the cyclosporine strategy step in the first CAMERA study (8). The primary outcome was radiographic erosive joint damage after 2 years. Secondary outcomes involved remission, improvements in disease activity and physical disability, and the need to add adalimumab to the treatment strategy. After the 2-year trial, prednisone was tapered and stopped, if possible.

In CAMERA-II, erosive joint damage after 2 years was limited as in the first CAMERA study, but it was significantly less in the strategy group receiving MTX and prednisone (n=117), compared to the strategy group receiving MTX and placebo (n=119). The cumulative probability plot of erosion scores at 2 years (Fig. 3) showed that 78% of all patients in the MTX and prednisone strategy group versus 67% in the MTX and placebo strategy group were still erosion-free; of those who did have erosions, erosion scores were higher in the MTX and placebo strategy group.

A somewhat higher number of patients had at least 1 period of sustained remission (remission for at least 3 months) in the MTX and prednisone strategy group: 72% *vs*. 61% in the MTX and placebo strategy group. The time until the first sustained remission was significantly shorter in the MTX and prednisone strategy group (6 months) than in the MTX and placebo strategy group (11 months).

The MTX and prednisone strategy also was significantly more effective in reducing disease activity and physical disability: faster and greater improvements compared to the improvements in the MTX and placebo strategy. During the trial, 14% of patients of the MTX and prednisone strategy required the adalimumab strategy step versus 36% of patients of the MTX and placebo strategy, not only a statistically significant result, but also clinically relevant to reduce cost.

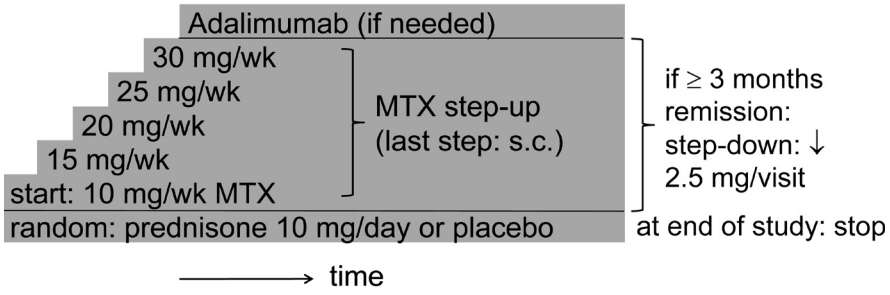
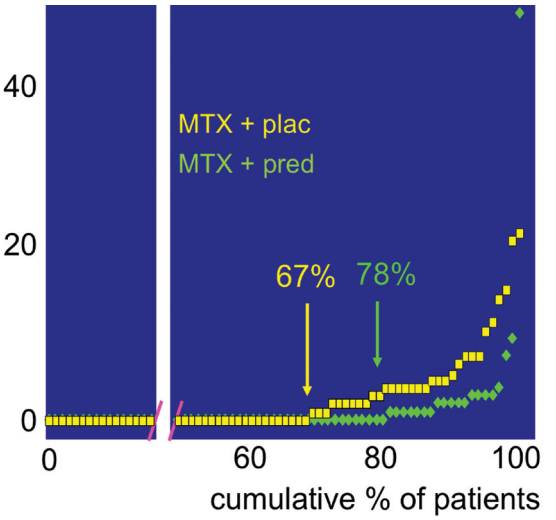


Fig. 2. The CAMERA-II tight control step-up strategy.
If not >20% improvement or remission, the strategy was intensified according to this scheme. If patients had remission for at least three months (sustained remission), MTX was reduced stepwise by 2.5 mg/week as long as patients met remission criteria; otherwise the dose of MTX was continued or increased again according to protocol. Prednisone was tapered at the end of the study and stopped, if possible.

Fig. 3. The cumulative probability plot of erosion scores in CAMERA-II at 2 years.
MTX+plac: the MTX-based strategy with placebo-prednisone;
MTX+pred: the MTX-based strategy with prednisone.
The plot displays the Sharp–van der Heijde scores for erosions (range, 0 to 280) on the Y-axis for individual patients, ranked along the x-axis (range 0-100% of patients). Each symbol is one patient. Of the patients in the MTX+pred strategy 78% *vs*. 67% in the MTX+plac strategy was still erosion free at 2 years and erosion scores of the latter strategy group were also generally higher. The median erosion score at 2 years was significantly less in the MTX+pred strategy.



Adverse events were similar in both groups, with exception of weight gain during the 2 year trial which was 2.9 kg in the MTX and prednisone strategy group *versus* 1.3 kg in the MTX and placebo strategy group, p=0.03. However, in an additional analysis, weight gain in the MTX and prednisone strategy seemed largely attributable to a reduction of disease activity (10), which was significantly greater in the MTX and prednisone strategy. The percentage of visits at which ≥1 adverse effect was reported was significantly lower with the MTX and prednisone strategy, 29% *versus* 35%. Mean non-fasting serum glucose levels after 2 years and the percentages of patients in each group who had higher (>1.0 mmol/L) serum glucose levels at 2 years compared with baseline values were not statistically significantly different between the 2 groups. In both groups, 1 patient developed diabetes.

In the MTX and prednisone strategy group, significantly less frequent nausea and significantly fewer elevations of serum transaminases were seen, likely attributable to the significantly lower mean MTX dose during the trial in this strategy group: 15 mg/week versus 19 in the MTX and placebo strategy group. The addition of 10 mg prednisone daily to the MTX-based tight control strategy had not led to bone loss. In both strategy groups – which received also a bisphosphonate, calcium and vitamin D – a small increase in lumbar BMD during the first year of treatment was found (11).

We concluded that inclusion of low-to-medium dose prednisone in an MTX-based tight control strategy in early RA improves patient outcomes and is MTX and anti-tumour necrosis factor therapy sparing.

Discussion

The results of the CAMERA studies show that with more intensive tight control strategies, early RA is controlled better, *i.e*. that outcomes are better. Furthermore, they corroborate the European League Against Rheumatism (EULAR) recommendation to initiate therapy in early RA with a synthetic DMARD, preferentially MTX, to which therapy a glucocorticoid may be added (Fig. 4) (12). The response to treatment at 6 months in the first CAMERA trial predicting significantly better 5-year clinical and radiographic outcome underlines the EULAR recommendation to perform a major switch in the treatment strategy in early RA if the target of treatment is not reached after 3–6 months (9).

The results document that very good treatment results are attainable in early RA with the inexpensive anchor drugs MTX and prednisone. This message is especially comforting in economically distressed times and for developing countries.

However, we do not advocate long-term use of 10 mg prednisone daily. Further research steps could be to investigate whether lower doses of prednisone would have similar efficacy when added to an intensive MTX-based tight control strategy, whether the symptomatic and disease modifying effects of glucocorticoids would also be present when initiated in patients with RA of longer duration than 2 years, and whether prednisone could be given for shorter periods without losing symptomatic and disease modifying effects. Other clinical trials showing disease modifying effects at lower doses of prednisone were not tight control studies and applied prednisone for 1 or 2 years in early RA, so do not answer these questions.

It is remarkable that glucocorticoids, which have been proven to be DMARDs in early RA, have not been included in the 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 (13, 14). This is in contrast to the EULAR 2010 recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying anti-rheumatic drugs (12).

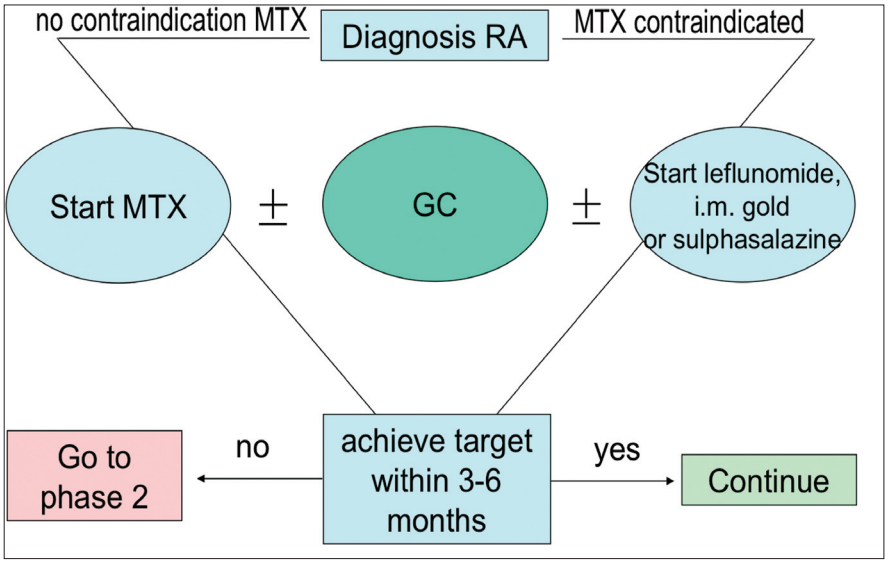


Fig. 4. The first phase of therapy as described in the 2010 EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying anti-rheumatic drugs (12). GC: glucocorticoid, *e.g*. prednisone; i.m. gold: intramuscular gold therapy; target: the treat-to-target goal: low disease activity or (preferentially) remission.

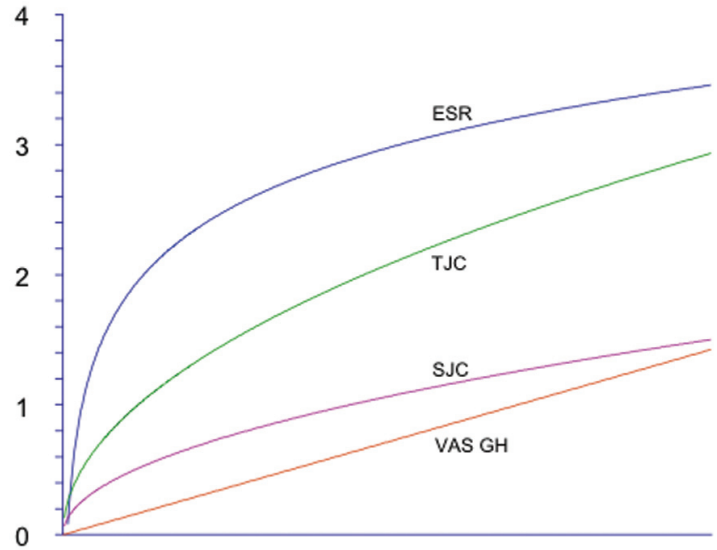


Fig. 5. Contribution to the DAS28 of the individual components of DAS28
Y-axis: units of the disease activity score assessing 28 joints (DAS28), x-axis: 0 - maximum range for each of the plotted variables. ESR: erythrocyte sedimentation rate (0-140 mm/1st hour); TJC: tender joint count (0-28); SJC: swollen joint count (0-28); VAS-GH: visual analogue scale for general health (0-100; 100=worst score). Tender joints have a contribution to DAS28 twice that of swollen joints; greatest changes in contribution of ESR to DAS28 are in lower ranges (and also in clinically not relevant, normal ranges) of ESR.
$DAS28 = 0.56 \sqrt{(TJC)} + 0.28 \sqrt{(SJC)} + 0.70 \ln(ESR) + 0.014 \text{ VAS GH}$

In our CAMERA studies, intensification of treatment was performed, if there was not >20% improvement in disease activity variables, at least SJC assessing 38 joints including ankles and feet, compared to the previous visit one month earlier. This was determined in a standardised way by using a computer program. In other studies, strategy changes often are based on the disease activity score of 28 joints (DAS28). For treat-to-target, we did not use the DAS28 – which has not properly been validated for this purpose, DAS28 has been validated for evaluation groups of patients – because of drawbacks of

the instrument. Joints of ankles and feet are not included in the DAS28. This seems on the group level (evaluation of group effects in clinical trials) not to be a problem, but on the individual patient's level it has been shown to potentially lead to misclassification of disease activity (15), *e.g.* resulting in false positive estimations of remission (16). In other words, increasing the risk of falsely assuming remission while there is active RA in ankles and feet. However, one could argue that in the absence of a generally accepted gold standard, there will always be disagreement on what constitutes remission, implicating that misclassification of remission thus is arbitrary.

Reliability of DAS28 in the individual patient can be questioned especially if there is concomitant fibromyalgia, as has been shown by others (17), or if there are tender points, even in the non-fibromyalgia range, as shown by our group (18), inducing false negative estimations of remission. In other words, increasing the risk of falsely assuming there is no remission of RA while in fact there is. To improve the specificity of assessing remission in individuals in DAS28-guided individual treat-to-target strategies, one could add to the DAS28 criterion of remission the criterion of absence of any swollen joint assessing all frequently in RA involved joints, or allowing only one swollen joint, like the Boolean definition of the 2011 remission criteria (19). When in doubt of arthritis, ultrasonography could be applied. Also, it is wise to not only look at the DAS28, but also at its individual components, which contribute to the DAS28 in unexpected ways (*e.g.* tender joints having an impact twice that of swollen joints (Fig. 5). This is not the case for the clinical disease activity index (CDAI) and the simplified disease activity index (SDAI), which again like DAS28 have the drawback of only assessing 28 joints (20).

In summary, the CAMERA studies have shown good results in the treatment of early RA patients with conventional anchor drugs, aiming for remission, applying a feasible, simple and face valid computer decision program.

Key message

Tight control treatment with the treat-to-target aim of remission using computer decision software is feasible and effective in early RA-patients with MTX-based strategies, especially when prednisone is added.

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