# Tight control and long-term prediction in rheumatoid arthritis

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# Tight control and long-term prediction in rheumatoid arthritis

Tight control en lange termijn voorspelling in reumatoïde artritis
(met een samenvatting in het Nederlands)

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**CONTENTS**

# INTRODUCTION

Chapter 1

## INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease that causes joint pain, progressive joint destruction and functional disability,[1-3] due to the combined effect of chronic synovitis and progressive joint damage.[4] Treatment of disease is important not only to alleviate signs and symptoms, but also to retard radiographic progression [5] and to prevent extra-articular manifestations, functional decline, and the need for joint surgery later on in the disease.[6]

This thesis describes studies conducted within the Utrecht Arthritis Cohort study group. This is a longstanding collaboration between the University Medical Center Utrecht and surrounding non-university hospitals* started in 1989 as the Utrecht Rheumatology Foundation (SRU). The first investigation of the SRU cohort showed that treatment with disease modifying anti-rheumatic drugs (DMARDs) should be initiated immediately after diagnosis of RA, instead of applying the traditional pyramid model. This latter strategy, starting with nonsteroidal anti-inflammatory drugs (NSAIDs) clearly was less effective compared with the early start of DMARDs.[7] The second study showed that among the investigated conventional DMARDs, methotrexate (MTX) scored the best regarding effectiveness and toxicity.[8] Therefore MTX was the anchor drug in the next study called Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA).[9] This tight control MTX-based strategy yielded very promising results (see below). This thesis is based on further studies on early RA treatment strategies.

In this first chapter, principles of tight control strategies of RA and of long-term prediction are described in short, followed by the outline of this thesis.

### Tight control treatment

Treatment strategies have evolved over the past decades. An immediate start of mono-DMARD therapy proved to be more efficacious than a delayed introduction of DMARDs according to the old-fashioned traditional pyramid model.[7, 10-12] Later on, combination DMARD strategies were applied. Since the beginning of the century, biological drugs became available as options for the treatment of RA. Recent therapeutic strategies based on combinations of DMARDs and/or biologicals are aimed at remission already in early stages of RA.[3, 13-15] (See Figure for the evolution of RA drug treatment.) The reason to do so is that RA is believed to be most responsive to treatment in the first months after diagnosis, the so called ‘window of opportunity’.[3, 16-18] Intensive treatment during this phase might lead to less severe RA later on, that is also more responsive to treatment, compared to applying intensive treatment later on in the course of disease.[16] So the new aim is to treat and control RA as soon as possible after the diagnosis.[19, 20] A strategy to reach this aim is so-called ‘tight control’.[21-23] Tight control can be defined as a treatment

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strategy with dose and strategy adjustments tailored to the disease activity of each individual RA patient aimed at a predefined level ('treat to target') of low disease activity or preferably remission within a reasonable period of time.[22]

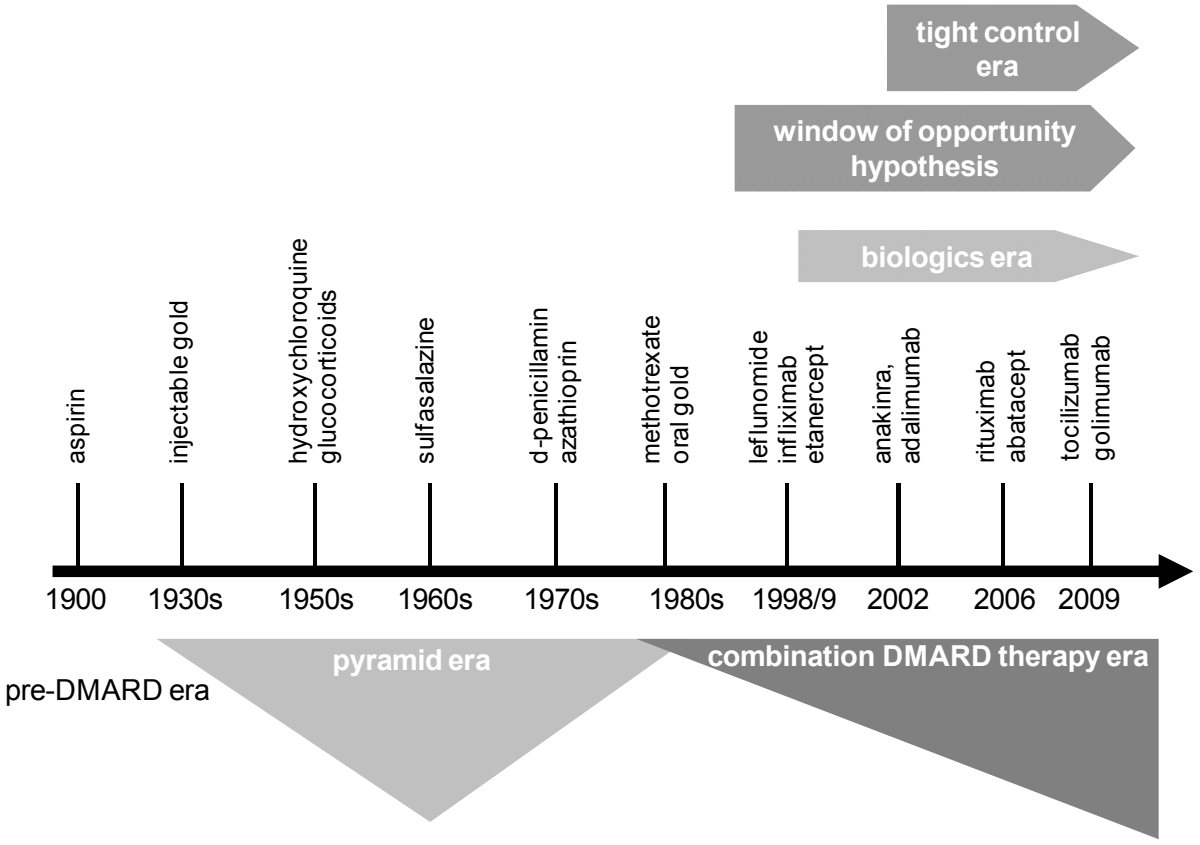


**Figure** Evolution of rheumatoid arthritis drug treatment.
* Years denote start of general use in clinical practice.

The CAMERA study was an early example of a tight control treatment strategy.[9] Patients were randomized to either a tight control MTX-based treatment strategy, based on computer guided monthly predefined response criteria, or to a conventional MTX-based strategy, based on regular clinical practice with three-monthly visits; both strategies were aiming at remission. Results showed an increased effectiveness of tight control compared to usual care strategy with MTX and more patients (respectively 50% vs. 37%) experienced at least one period of remission.

Based on studies like CAMERA, current recommendations for the treatment of (early) RA suggest that all patients should start with DMARD treatment in a tight control fashion as soon as the diagnosis is made.[3] MTX is considered as the DMARD of first choice in starting treatment and the anchor drug in RA. Advantages of MTX are its low costs, proven efficacy in RA, relatively fast response, high tolerability, its effect of slowing down joint damage; it is administrable both orally and subcutaneously in a wide range of dosages (2.5-30 mg).[24-27] MTX could be combined with glucocorticoids from start of therapy. Glucocorticoids are considered as DMARDs because they are able to reduce the

progression of joint damage;[29, 30] the combination with other conventional DMARDs, especially MTX, has been proven to be effective. If the treatment target (i.e. remission or low disease activity) is not achieved within the first months, as next step another conventional DMARD could be added or a biological DMARD.[3, 28] The CAMERA-II study described in this thesis was based on these principles.

**Long-term prediction**

To optimally apply the tight control principle within the 'window of opportunity', prediction of the outcome of RA early in the disease could aid in choosing the most adequate DMARD strategy to start with. Step-down strategies (starting with combination treatment with DMARDs, tapering down in case of clinical response),[14, 31] step-up strategies (starting one DMARD and adding DMARDs in case of insufficient effect)[32] and hybrids of these strategies are used in the treatment of RA. Starting directly after diagnosis with a step-down strategy potentially has the advantage of an intensive early treatment within the 'window of opportunity' in patients with a predicted poor prognosis, but vice versa the disadvantage of possible overtreatment in patients with a predicted good prognosis. In contrast, step-up strategies could lead to initial undertreatment in patients with a poor diagnosis.

Predictors have been identified that are related to a negative long-term outcome regarding disease activity and radiographic joint damage. These predictors are serum autoantibodies, i.e. rheumatoid factor (RF) and anticitrullinated autoantibodies (antiCCP), high baseline disease activity levels, baseline radiographic damage, higher age, female gender, and smoking.[33-41] Prediction models to facilitate treatment decisions in clinical practice based on these known predictors of long-term outcome still need improvement.[41-43]

A relatively new predictor of long-term outcome of RA is early response to treatment. Patients responding well to treatment in an early phase of the disease, within the 'window of opportunity' seem to have a better long-term treatment outcome regarding disease activity and radiographic damage.[44, 45] This is compatible with hypotheses on the benefits of tight control.

In tight control strategies, often disease activity indices are used to treat patients to target, preferentially remission, for better long-term outcome regarding disease activity and radiographic joint damage. So the indices, next to reflecting the current state of disease activity, predict long-term outcome. Frequently used indices are the disease activity score based on 28 joints (DAS28), the clinical disease activity index (CDAI) and simplified disease activity index (SDAI).[46, 47]

Biomarkers assessed in an early phase of the disease also potentially can predict the long-term outcome of RA. Results of current biomarkers in this respect are conflicting; ongoing research is warranted.[48-58]

## OUTLINE OF THIS THESIS

The aim of this thesis is to optimise the tight control principle in RA and to gain knowledge on possible predictors of outcome measurements of RA on the short-term as well as the long-term of the disease.

### Section I: tight control treatment

The first issue addressed in this thesis is the principle of tight control in RA (**chapter 2**). As tight control is used more frequently now in the treatment of (early) RA patients, it was investigated to what extend tight control can be considered as an efficacious and feasible principle in the treatment of RA patients. This was studied by reviewing published randomized trials available in patients with early RA.

Tight control treatment means application of more intensive treatment strategies. **Chapter 3** describes whether a tight control treatment strategy also leads to more adverse events and more toxicity when compared to conventional treatment. To evaluate this possibility a broad spectrum of toxicity was evaluated and compared in early RA patients treated either according to the intensive (tight control) or conventional MTX-based treatment strategy (an exploration of the CAMERA study). In addition, it was analyzed whether possible associations existed between baseline characteristics (clinical, laboratory as well as patient characteristics) and MTX related withdrawal and liver toxicity during follow-up.

For the tight control principle, several strategies can be applied. The anchor drug in RA treatment is MTX and in case of insufficient effect, different next strategy steps are possible, e.g. adding of DMARDs. In **chapter 4** the effectiveness of the used next treatment strategy steps within the tight control treatment strategy of the CAMERA trial was investigated. If needed, after reaching the maximum (tolerable) oral MTX dose, next treatment strategy steps were the subcutaneous MTX (scMTX) strategy step and thereafter the cyclosporine strategy step (adding cyclosporine with a simultaneous reduction of the MTX dose of max 15 mg/wk).

In most studies, only short-term effectiveness of tight control strategies in early RA patients is documented. However, it is also important to know the long-term effect of a tight control strategy. In **chapter 5**, the 5 year results (3 year follow-up data) of the CAMERA study are described. After the 2-year trial, patients were yearly followed with no predefined treatment prescriptions anymore. It was studied whether the effects of the MTX-based tight control strategy during the first 2 years were still apparent on the long-term. Besides tight control long-term effectiveness, the (added) predictive value of an early response to treatment for long-term outcome of patients with respect to disease activity and progression of radiographic joint damage was examined.

Within the current treatment of RA, the development of tight control strategies is still ongoing. The existing tight control strategies are effective, but still leave room for improvement. The challenge is to develop a strategy that is very effective as well as cheap, so it could be generally applicable (i.e. also for developing countries). In **chapter 6**, the second Computer Assisted Management in Early Rheumatoid Arthritis trial (CAMERA-II) is described. In this randomized, placebo-controlled, double-blind, prospective, multi-centre, two-year treatment strategy trial it was investigated whether adding prednisone to a MTX-based tight control strategy from start of treatment of early RA is more effective than a MTX-based tight control strategy without prednisone (as used in CAMERA).

**Section II: long-term prediction**

For an optimal treatment strategy it could be important to be able to predict the outcome for the individual RA patient. This would help to prevent under- or overtreatment of RA patients. A step could be to try to predict the MTX dose needed to obtain an optimal response for each individual patient, i.e. the dose at which a further dose increase step would not clinically relevantly decrease disease activity anymore. In **chapter 7** these 'lowest optimally effective doses' (LOEDs) for individual patients were determined. If LOED could be predicted reliably it could serve as a starting dose, as target dose to reach as soon as possible, and as a switching dose cut-off to consider adding other DMARDs to the strategy if disease activity would still be too high. This chapter describes to what extent LOEDs and the level of disease activity reached could be predicted in individual patients.
In tight control strategies, regular monitoring of disease activity is necessary to reach the aim of low disease activity or remission in each individual RA patient. Although monitoring instruments assess the current state of the disease activity, they are also important for prediction of future joint damage. One of the most generally used instruments in clinical trials as well as daily practice is the DAS28. However, this instrument is basically developed for group assessments; the validity of the use of this index to assess remission and to predict outcome (i.e. joint destruction) in the individual patient is not yet clear. Within the next two chapters, the usage of DAS28 as a tight control instrument is evaluated. In the first chapter (**chapter 8**) the influence of coexistence of tender points in patients with RA on the DAS28 was described. It is known that presence of tender points can lead to a discrepancy between the DAS28 and the physician's impression of disease activity in clinical practice.
With the tight control principle, treatment is tailored to the disease activity level of each individual patient. In **chapter 9**, the results are given of a study into the longitudinal relation between disease activity as assessed with DAS28 (excluding joints of feet) and radiographic damage in different patient groups, classed according whether they had predominantly progression in joints of hands or joints of feet. If the relation of DAS28 and long-term outcome would be different for these radiographic progression groups, not only assessment of actual disease activity, but also the prediction of future radiographic damage are less reliable using DAS28, if RA involves joints of feet.

In the last two chapters, the predictive value of different biomarkers was evaluated. Biomarkers might be good predictors, directly reflecting the current state of disease activity and radiographic damage of patients with RA, which both are known predictors of long-term outcome. First, the possible prediction of long-term outcome by usage of bone and cartilage biomarkers, determined early in the disease, was analysed (**chapter 10**). It was investigated whether the biomarkers C2C, C1,2C, CS846, and CPII could predict the long-term radiographic and clinical outcome in patients with early RA.
Finally, in **chapter 11** an algorithm of biomarkers was investigated, evaluating the association of this algorithm with RA disease activity. If this algorithm would be a good predictor, the potential arises to enhance patient assessment and to use it along already existing monitor instruments for tight control.

## REFERENCES


1. Scott DL, Symmons DP, Coulton BL, et al. Long-term outcome of treating rheumatoid arthritis: results after 20 years. Lancet 1987;1:1108-11.
2. Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. Lancet 2010;376:1094-108.
3. Smolen JS, Landewe R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis 2010;69:964-75.
4. Pollard L, Choy EH, Scott DL. The consequences of rheumatoid arthritis: quality of life measures in the individual patient. Clin Exp Rheumatol 2005;23:S43-S52.
5. Raza K, Buckley CE, Salmon M, et al. Treating very early rheumatoid arthritis. Best Pract Res Clin Rheumatol 2006;20:849-63.
6. Verstappen SM, Hoes JN, Ter Borg EJ, et al. Joint surgery in the Utrecht rheumatoid arthritis cohort: The effect of treatment strategy. Ann Rheum Dis 2006;65:1506-11.
7. van der Heide A, Jacobs JW, Bijlsma JW, et al. The effectiveness of early treatment with "second-line" antirheumatic drugs. A randomized, controlled trial. Ann Intern Med 1996;124:699-707.
8. van Jaarsveld CH, Jacobs JW, van der Veen MJ, et al. Aggressive treatment in early rheumatoid arthritis: a randomised controlled trial. On behalf of the Rheumatic Research Foundation Utrecht, The Netherlands. Ann Rheum Dis 2000;59:468-77.
9. Verstappen SM, Jacobs JW, van der Veen MJ, et al. Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open label trial). Ann Rheum Dis 2007;66:1443-9.
10. Case JP. Old and new drugs used in rheumatoid arthritis: a historical perspective. Part 1: the older drugs. Am J Ther 2001;8:123-43.
11. Nell VP, Machold KP, Eberl G, et al. Benefit of very early referral and very early therapy with disease-modifying anti-rheumatic drugs in patients with early rheumatoid arthritis. Rheumatology (Oxford) 2004;43:906-14.
12. Smolen JS, Aletaha D, Machold KP. Therapeutic strategies in early rheumatoid arthritis. Best Pract Res Clin Rheumatol 2005;19:163-77.
13. Capell HA, Madhok R, Porter DR, et al. Combination therapy with sulfasalazine and methotrexate is more effective than either drug alone in patients with rheumatoid arthritis with a suboptimal response to sulfasalazine: results from the double-blind placebo-controlled MASCOT study. Ann Rheum Dis 2007;66:235-41.
14. Landewe RB, Boers M, Verhoeven AC, et al. COBRA combination therapy in patients with early rheumatoid arthritis: long-term structural benefits of a brief intervention. Arthritis Rheum 2002;46:347-56.
15. Wilske KR, Healey LA. Remodeling the pyramid--a concept whose time has come. J Rheumatol 1989;16:565-7.
16. Boers M. Understanding the window of opportunity concept in early rheumatoid arthritis. Arthritis Rheum 2003;48:1771-4.
17. Knevel R, Schoels M, Huizinga TW, et al. Current evidence for a strategic approach to the management of rheumatoid arthritis with disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis 2010;69:987-94.
18. Smolen JS, Aletaha D, Bijlsma JW, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis 2010;69:631-7.
19. Moreland LW, Russell AS, Paulus HE. Management of rheumatoid arthritis: the historical context. J Rheumatol 2001;28:1431-52.
20. Wolfe F, Cush JJ, O'Dell JR, et al. Consensus recommendations for the assessment and treatment of rheumatoid arthritis. J Rheumatol 2001;28:1423-30.
21. Schipper LG, van Hulst LT, Grol R, et al. Meta-analysis of tight control strategies in rheumatoid arthritis: protocolized treatment has additional value with respect to the clinical outcome. Rheumatology (Oxford) 2010;49:2154-64.

22. Bakker MF, Jacobs JW, Verstappen SM, et al. Tight control in the treatment of rheumatoid arthritis: efficacy and feasibility. Ann Rheum Dis 2007;66 Suppl 3:iii56-60.
23. Mease PJ. Improving the routine management of rheumatoid arthritis: the value of tight control. J Rheumatol 2010;37:1570-8.
24. Braun J, Rau R. An update on methotrexate. Curr Opin Rheumatol 2009;21:216-23.
25. Visser K, van der Heijde D. Optimal dosage and route of administration of methotrexate in rheumatoid arthritis: a systematic review of the literature. Ann Rheum Dis 2008;68:1094-9.
26. 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.
27. Salliot C, van der Heijde D. Long-term safety of methotrexate monotherapy in patients with rheumatoid arthritis: a systematic literature research. Ann Rheum Dis 2009;68:1100-4.
28. Gorter SL, Bijlsma JW, Cutolo M, et al. Current evidence for the management of rheumatoid arthritis with glucocorticoids: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis 2010;69:1010-4.
29. Bijlsma JW, Hoes JN, Van Everdingen AA, et al. Are glucocorticoids DMARDs? Ann N Y Acad Sci 2006;1069:268-74.
30. Kirwan JR, Bijlsma JW, Boers M, et al. Effects of glucocorticoids on radiological progression in rheumatoid arthritis. Cochrane.Database.Syst.Rev. 2007:CD006356.
31. Boers M, Verhoeven AC, Markusse HM, et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet 1997;350:309-18.
32. Grigor C, Capell H, Stirling A, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. Lancet 2004;364:263-9.
33. Vazquez I, Graell E, Gratacos J, et al. Prognostic markers of clinical remission in early rheumatoid arthritis after two years of DMARDs in a clinical setting. Clin Exp Rheumatol 2007;25:231-8.
34. Machold KP, Stamm TA, Nell VP, et al. Very recent onset rheumatoid arthritis: clinical and serological patient characteristics associated with radiographic progression over the first years of disease. Rheumatology (Oxford) 2007;46:342-9.
35. Smolen JS, van der Heijde DM, St Clair EW, et al. Predictors of joint damage in patients with early rheumatoid arthritis treated with high-dose methotrexate with or without concomitant infliximab: results from the ASPIRE trial. Arthritis Rheum 2006;54:702-10.
36. van der Heide A, Remme CA, Hofman DM, et al. Prediction of progression of radiologic damage in newly diagnosed rheumatoid arthritis. Arthritis Rheum 1995;38:1466-74.
37. Wessels JA, van der Kooij SM, le Cessie S, et al. A clinical pharmacogenetic model to predict the efficacy of methotrexate monotherapy in recent-onset rheumatoid arthritis. Arthritis Rheum 2007;56:1765-75.
38. Schmajuk G, Schneeweiss S, Katz JN, et al. Treatment of older adult patients diagnosed with rheumatoid arthritis: Improved but not optimal. Arthritis Rheum 2007;57:928-34.
39. Mancarella L, Bobbio-Pallavicini F, Ceccarelli F, et al. Good clinical response, remission, and predictors of remission in rheumatoid arthritis patients treated with tumor necrosis factor-alpha blockers: the GISEA study. J Rheumatol 2007;34:1670-3.
40. Welsing PM, Landewe RB, van Riel PL, et al. The relationship between disease activity and radiologic progression in patients with rheumatoid arthritis: a longitudinal analysis. Arthritis Rheum 2004;50:2082-93.
41. Bansback N, Young A, Brennan A, et al. A prognostic model for functional outcome in early rheumatoid arthritis. J Rheumatol 2006;33:1503-10.
42. Vastesaeger N, Xu S, Aletaha D, et al. A pilot risk model for the prediction of rapid radiographic progression in rheumatoid arthritis. Rheumatology (Oxford) 2009;48:1114-21.
43. Visser K, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, et al. A matrix risk model for the prediction of rapid radiographic progression in patients with rheumatoid arthritis receiving different dynamic treatment strategies: post hoc analyses from the BeSt study. Ann Rheum Dis 2010;69:1333-7.

44. Verstappen SM, van Albada-Kuipers GA, Bijlsma JW, et al. A good response to early DMARD treatment of patients with rheumatoid arthritis in the first year predicts remission during follow up. Ann Rheum Dis 2005;64:38-43.
45. Aletaha D, Funovits J, Keystone EC, et al. Disease activity early in the course of treatment predicts response to therapy after one year in rheumatoid arthritis patients. Arthritis Rheum 2007;56:3226-35.
46. Prevoo ML, van 't Hof MA, Kuper HH, et al. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38:44-8.
47. Aletaha D, Smolen JS. The Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI) to monitor patients in standard clinical care. Best Pract Res Clin Rheumatol 2007;21:663-75.
48. Gonzalez-Alvaro I, Ortiz AM, Tomero EG, et al. Baseline serum RANKL levels may serve to predict remission in rheumatoid arthritis patients treated with TNF antagonists. Ann Rheum Dis 2007;66:1675-8.
49. Hammer HB, Odegard S, Syversen SW, et al. Calprotectin (a major S100 leukocyte protein) predicts 10-year radiographic progression in patients with rheumatoid arthritis. Ann Rheum Dis 2010;69:150-4.
50. Hashimoto J, Garnero P, van der Heijde D, et al. A combination of biochemical markers of cartilage and bone turnover, radiographic damage and body mass index to predict the progression of joint destruction in patients with rheumatoid arthritis treated with disease-modifying anti-rheumatic drugs. Mod Rheumatol 2009;19:273-82.
51. Knudsen LS, Klarlund M, Skjodt H, et al. Biomarkers of inflammation in patients with unclassified polyarthritis and early rheumatoid arthritis. relationship to disease activity and radiographic outcome. J Rheumatol 2008;35:1277-87.
52. Landewe RB, Geusens P, van der Heijde DM, et al. Arthritis instantaneously causes collagen type I and type II degradation in patients with early rheumatoid arthritis: a longitudinal analysis. Ann Rheum Dis 2006;65:40-4.
53. Lindqvist E, Eberhardt K, Bendtzen K, et al. Prognostic laboratory markers of joint damage in rheumatoid arthritis. Ann Rheum Dis 2005;64:196-201.
54. Marotte H, Gineyts E, Miossec P, et al. Effects of infliximab therapy on biological markers of synovium activity and cartilage breakdown in patients with rheumatoid arthritis. Ann Rheum Dis 2009;68:1197-200.
55. Syversen SW, Haavardsholm EA, Boyesen P, et al. Biomarkers in early rheumatoid arthritis: longitudinal associations with inflammation and joint destruction measured by magnetic resonance imaging and conventional radiographs. Ann Rheum Dis 2010;69:845-50.
56. van Tuyl LH, Voskuyl AE, Boers M, et al. Baseline RANKL:OPG ratio and markers of bone and cartilage degradation predict annual radiological progression over 11 years in rheumatoid arthritis. Ann Rheum Dis 2010;69:1623-8.
57. Visvanathan S, Marini JC, Smolen JS, et al. Changes in biomarkers of inflammation and bone turnover and associations with clinical efficacy following infliximab plus methotrexate therapy in patients with early rheumatoid arthritis. J Rheumatol 2007;34:1465-74.
58. Young-Min S, Cawston T, Marshall N, et al. Biomarkers predict radiographic progression in early rheumatoid arthritis and perform well compared with traditional markers. Arthritis Rheum 2007;56:3236-47.

Chapter 2

# Tight control in the treatment of rheumatoid arthritis: efficacy and feasibility

On behalf of the Utrecht Arthritis Cohort study group

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## ABSTRACT

### Objective

To evaluate available evidence on the efficacy and feasibility of the new concept of tight control in randomized trials in patients with rheumatoid arthritis (RA). Tight control is a treatment strategy tailored to the individual RA patient with the aim to achieve within a certain period of time a predefined level of low disease activity or remission.

### Methods

The literature base Pubmed was searched yielding 3 trials: the FIN-RACo trial, the TICORA study, the BeSt study, next to the CAMERA study.

### Results

Tight control resulted in more improvement and a higher percentage of patients meeting the presetted aim of low disease activity or remission when compared to the control intervention. In the FIN-RACo trial, analysing the subset of patients completing the study, 68% in the tight control group achieved remission (DAS28 <2.6) versus 41% in the contrast group ($p<0.001$). In the TICORA study 65% of patients in the tight control group versus 16% of the contrast group received remission, based on DAS <1.6 ($p<0.0001$). In the CAMERA study, 50% of patients in the tight control strategy using a computer decision model received remission, versus 37% in the contrast strategy ($p=0.029$). The BeSt study consisted of only tight control groups aimed at a DAS<1.6; remission was achieved in 38 - 46% of patients. This is higher than the range of remission in earlier trials of 13 - 36%.

### Conclusion

Tight control aiming for low disease activity or even better still, remission, seems a promising option in treating RA patients in clinical trials and probably daily practice too.

## INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease that causes joint pain, progressive joint destruction and functional disability,[1] due to the combined effect of chronic synovitis and progressive joint damage.[2] Treatment of disease, already in the first months of synovitis is important to retard radiographic progression.[3] This window of opportunity suggests that disease activity in patients with early RA is less severe, is characterized by a smaller load of inflammatory cells, and is more responsive to treatment. So aggressive treatment during this phase is more likely to succeed than is the same treatment applied later in the course of disease,[4] when possibly autoantigens from damaged joints fuel the disease. Therefore it is important that RA should be treated and controlled as soon as possible after the diagnosis and that this control should be maintained for as long as possible, consistent with patient safety.[5, 6]

In the past, the traditional (pyramid model) treatment therapy started with nonsteroidal anti-inflammatory drugs (NSAIDs). If the treatment was insufficiently effective, second-line antirheumatic drugs or disease modifying anti-rheumatic drugs (DMARDs) were added. However, an immediate start of DMARDs proved to be more efficacious than a delayed introduction of DMARDs in the disease progress of RA.[7, 8] More recent therapeutic strategies are based on (combinations of) DMARDs to control inflammation in the critical early stages of RA.[9-11] Glucocorticoids, which also can be considered as DMARDs because they are able to reduce the progression of joint damage, have been included in DMARD combination treatments of RA.[12, 13]

The most current treatment strategies are combination therapies with conventional DMARDs and biologicals.[14] With these therapies, not only improvement in signs and symptoms but also low disease activity and even remission come within reach. Overall, a paradigm shift is observed in the trials of RA: treatment is more frequently aimed at low disease activity or remission in each individual patient,[15, 16] instead of randomizing groups into standardised therapies. This new way of treatment is called “tight control”. The definition of tight control can be: A treatment strategy tailored to the disease activity of individual RA patients with the aim to achieve within a reasonable period of time a predefined level of low disease activity or preferably remission.

The aim of this evaluation is to investigate how effective and feasible tight control is.

## PATIENTS AND METHODS

A Pubmed search was performed looking for studies which used a predefined level of disease activity or remission as treatment aim using the following terms: rheumatoid arthritis, randomized trial, treatment strategy, low disease activity, remission, and tight control. Abstracts were screened for the tight control principle. The search yielded 3 studies, in chronological order, the FIN-RACo trial,[17, 18] the TICORA study,[19] the BeSt study,[20-22] next to the CAMERA study.[23] Different outcome parameters and study designs

prohibited pooling of the effects of these studies. Therefore, study characteristics including the aim of the study (low disease activity or remission), time schedule, the method of evaluation of the individual patient, the adaptation of the medication, and the results of the studies will be described.

## RESULTS

Table 1 gives an overview of the inclusion criteria and the different treatments used in the four studies. Except for the TICORA study, disease duration was less than 2 years, and the patients had to fulfil the American College of Rheumatology (ACR) classification criteria for RA for inclusion. Except for the CAMERA study, the inclusion criteria contained active disease and an age over 18 years.

### FIN-RACo

The Finnish Rheumatoid Arthritis Combination Therapy (FIN-RACo) study [18] is a multicentre, randomized open-parallel group treatment trial in which 195 patients were included in the period between 1993 and 1995. The goal of the study was to compare the effects of the combination therapy with DMARDs with those of mono DMARD therapy in patients with early RA. Based on the evaluation of the individual patient, the medication was intensified after 3 months in the combination group if there was less than 50% improvement on 2 out of 3 variables: swollen joint score (SJC), tender joint score (TJC), and erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP). In the mono DMARD group the medication was intensified if there was less than 25% improvement after 6 months. The aim of the FIN-RACo study was remission, defined both with the ACR remission criteria,[24] and as a Disease Activity Score including the 28-joint count (DAS28 [25]) <2.6, and good treatment response according to criteria of the European League Against Rheumatism (EULAR).[26] After 2 years, more patients in the combination group compared with the mono DMARD group had met the ACR remission criteria (37% vs. 18%, p=0.003). Analysing the subset of patients completing the study, 68% vs. 41% met the DAS28 remission criterion (p<0.001) and 67% vs. 27% (p<0.001) the criteria of sustained good treatment response, respectively. Combination therapy thus was better and not more hazardous than single treatment in induction of remission in early RA. Combination therapy as a tight control strategy in patients with early RA aiming for remission seems to be more efficacious than monotherapy.[17]

### TICORA

The Tight Control of Rheumatoid Arthritis (TICORA) study [19] is a single-blind randomized controlled trial in which 111 patients, some with disease duration up to 5 years, were included between 1999 and 2001. The goal of the study was to compare tight controlled treatment versus routine treatment. The evaluation and strategy of medication adaptations and escalations was based on an objective disease activity score in the individual treated,

| Study | Interventions / groups | n | Medication at start | Frequency of assessment | Inclusion criteria | Disease duration |
|---|---|---|---|---|---|---|
| FIN-RACo | combination therapy* | 97 | SSZ, MTX, HCQ, predn | 3 months (variables) | ARA criteria RA, 18-65 yr, symptoms <2 yr, active disease ≥3 SJ and 3 of: ≥28 mm/h ESR or ≥19 mg/l CRP, ≥29 min ms, >5 SJ or >10 TJ | <2 years |
| | mono therapy | 86 | SSZ (+/-) predn | 3/6 months (clinical decision, variables) | | |
| TICORA | intensive management* | 55 | DMARD, i.a. steroid | 1 month (DAS) | 18-75 yr, disease duration <5yr, active disease (DAS>2.4) | <5 years |
| | routine management | 55 | DMARD mono | 3 months (clinical decision) | | |
| BeSt | sequential mono therapy* | 126 | MTX | 3 months (DAS44) | ACR criteria RA, ≥18 yr, disease duration ≤2 yr, active disease: ≥6 of 66 SJ, ≥6 of 68 TJ, ≥28 mm/h ESR, ≥20 mm VAS-GH | ≤2 years |
| | step-up mono therapy* | 121 | MTX | 3 months (DAS44) | | |
| | initial combi therapy + h.d. predn* | 133 | MTX, SSZ, predn | 3 months (DAS44) | | |
| | initial combi therapy + infliximab* | 128 | MTX, infliximab | 3 months (DAS44) | | |
| CAMERA | intensive strategy group* | 151 | MTX | 1 month (computer decision program) | ACR criteria RA, >16 yr, early RA (<1 yr) | ≤1 year |
| | conventional strategy group | 148 | MTX | 3 months (clinical decision) | | |

**Table 1** Characteristics of the tight control studies.
* = based on tight control treatment
FIN-RACo= Finnish rheumatoid arthritis combination therapy; TICORA= Tight control of rheumatoid arthritis; BeSt= Behandel strategieën; CAMERA= Computer assisted management of early rheumatoid arthritis; combi= combination therapy; h.d. predn= high-dose prednisone; SSZ= sulfasalazine; MTX= methotrexate; HCQ= hydroxychloroquine; predn= prednisone; DMARD= disease modifying anti-rheumatic drug; i.a. steroid= intra articular steroid; DAS= disease activity score; ARA criteria RA= American Rheumatism Association criteria for rheumatoid arthritis; yr= year(s); SJ= swollen joints; ESR= erythrocyte sedimentation rate; CRP= C-reactive protein; ms= morning stiffness; TJ= tender joints; ACR criteria RA= American College of Rheumatism criteria for rheumatoid arthritis; VAS-GH= visual analogue scale global health.

tight control group and evaluated in the routine group by the subjective opinion of the clinician. Outcome of the TICORA study was the mean fall in disease activity score, the number of patients with good response (defined as a DAS28 <2.4 after 2 years and a fall in this score from baseline of more than 1.2), and the percentage of patients in remission. The results of TICORA showed that the mean fall in the disease activity score was higher in the tight control group than in the routine group (-3.5 vs. -1.9, p<0.0001). Compared with routine care, tight control patients had a good response (82% vs. 44%, p<0.0001) or remission (DAS28 <1.6) (65% vs. 16%, p<0.0001). Next to disease activity, also radiographic disease progression, physical function, and quality of life in the tight control group were more favourable than in the routine care group, at no additional financial costs.

**BeSt**

The Behandel Strategieën (BeSt) study [21] is a multicentre randomized open clinical trial in which 508 patients with early active RA were included between 2000 and 2002. The goal of the study was to compare four treatment strategies: sequential mono therapy, step-up combination therapy, and initial combination therapy with high-dose prednisone or infliximab. Evaluation of the individual patients was in all 4 groups based on Disease Activity Score 44-joint counts (DAS44).[27] Medication was intensified if DAS44 exceeded 2.4 and decreased if DAS ≤2.4 for the period of 6 months. The outcomes of the BeSt study were functional ability, radiographic joint damage, and the percentages of patients meeting the criterion of low disease activity (DAS44 ≤2.4) or remission (DAS44 <1.6). After 1 year patients of the initial combination therapy including either prednisone or infliximab had earlier functional improvement and less radiographic damage than those on sequential monotherapy or step-up therapy. After 2 years of treatment, these differences seem to disappear and no statistically significant differences were seen between the groups in the percentage of patients in remission (46%, 38%, 41% respectively 42%, p=0.69). It seems that in patients with early active RA, remarkable clinical improvement and suppression of joint damage progression can be achieved with frequent, objective treatment adjustments.[20, 22]

**CAMERA**

The Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA) study [23] is a randomized prospective multicentre trial in which 299 patients with early RA were allocated between 1999 and 2003. The goal of the study was to compare intensive with conventional treatment, both strategies aiming for remission. This is the only tight control study comparing the same treatment in a tight control scheme and a conventional scheme. In the intensive (tight control) group, decisions on therapy were made more frequently and with the use of an objective computer decision program evaluation in the individual patient. The computer decision model was based on the SJC, TJC, ESR, and the visual analogue scale (VAS) general well-being. Medication was intensified if less than 20% improvement has occurred after each month of assessment, unless remission was reached. In the conventional treatment group every three months the decision on medication was made by

the clinician, mirroring common practice, but also intensifying the medication when clinically indicated, as judged by the attending physician. Remission was defined as no swollen joints and 2 out of 3 of the following variables: number of tender joints ≤3, ESR ≤20 mm/hr$^{1st}$, and VAS general well-being ≤20 mm. After 2 years, 50% of the patients in the intensive treatment group versus 37% in the conventional group (p=0.029) had been in remission for at least 6 months during the study. These results show that tailoring of treatment to the individual patient by a computerized decision program, aiming for remission, is more beneficial than the strategy mirroring daily practice also aiming for remission. Therefore, this strategy could be a helpful tool in daily clinical practice.

## DISCUSSION

In the present report efficacy and feasibility of tight control in randomized trials in patients with early RA is evaluated. It seems that tight control and the aims of low disease activity and remission are feasible and favourable.

Of the four studies, TICORA and CAMERA give the best insight into tight control, since they compared a tight control group with a routine or conventional group. Of these two studies the CAMERA might offer the best comparison, because in this study the same medication in the same dosage has been used in the tight control group and the conventional groups. In contrast, all intervention groups in the BeSt study make use of the concept of tight control so there is no comparison group. In the FIN-RACo study, the efficacy of a less intensive level of tight control was compared with that of a more intensive level; the latter yielded the best results.

In the evaluated studies different protocols in the tight control groups were used to make therapy choices and changes. In both the TICORA study and the BeSt study therapy changes were based on the DAS score. In the FIN-RACo study as well as the CAMERA study therapy changes were based on the percentage improvement in disease activity of the individual patient. In contrast to FIN-RACo, dose adjustments in the CAMERA study were based on a predefined scheme and decided on a computer decision program which increases objectivity. For the future, the protocol for therapy changes in studies used for tight control should be standardized, enabling comparison and pooling different study outcomes.

The aim in all four studies was the number of patients in remission. The range of remission rates in the tight control groups was significantly better than in the comparison groups (50 - 68% remission vs. 16 - 41%) or, to make a comparison with historical controls for the groups in the BeSt study (38 - 46% remission), the percentages of remission in earlier trials were within a range of 13 - 36%.[16, 28, 29] However, different definitions were used to define remission and tight control as a new paradigm needs the use of uniform criteria of low disease activity or remission. Sustained remission is currently, with the arrival of the combination DMARD therapy and the biologicals, an achievable goal in clinical practice.[30, 31] Before the main goal of treatment was to achieve remission, the ACR20/50/70

improvement criteria were standard for controlled clinical trials. But they do not give any information about the current status of disease activity. A patient could be improved a lot and still have active disease.[32] Criteria of low disease activity have the drawback that patients may still have progression of radiographic joint damage.[33] Therefore remission rather than low disease activity should be our treatment goal today.[34] On the other hand, even when remission should be the best feasible outcome measure, this term is still poorly defined and various remission criteria mirror different degrees of disease activity.[31, 35] In three out of four evaluated studies, the DAS [27] remission criteria were used to define remission. However, for use in individual patients, the DAS has not been validated. It is rather sensitive for changes in ESR in the (nearly) normal range, see Figure 1.[36] This Figure also shows that the relative contribution of tender joints to the DAS28 score is much higher than that of swollen joints, which is a more specific feature of RA.

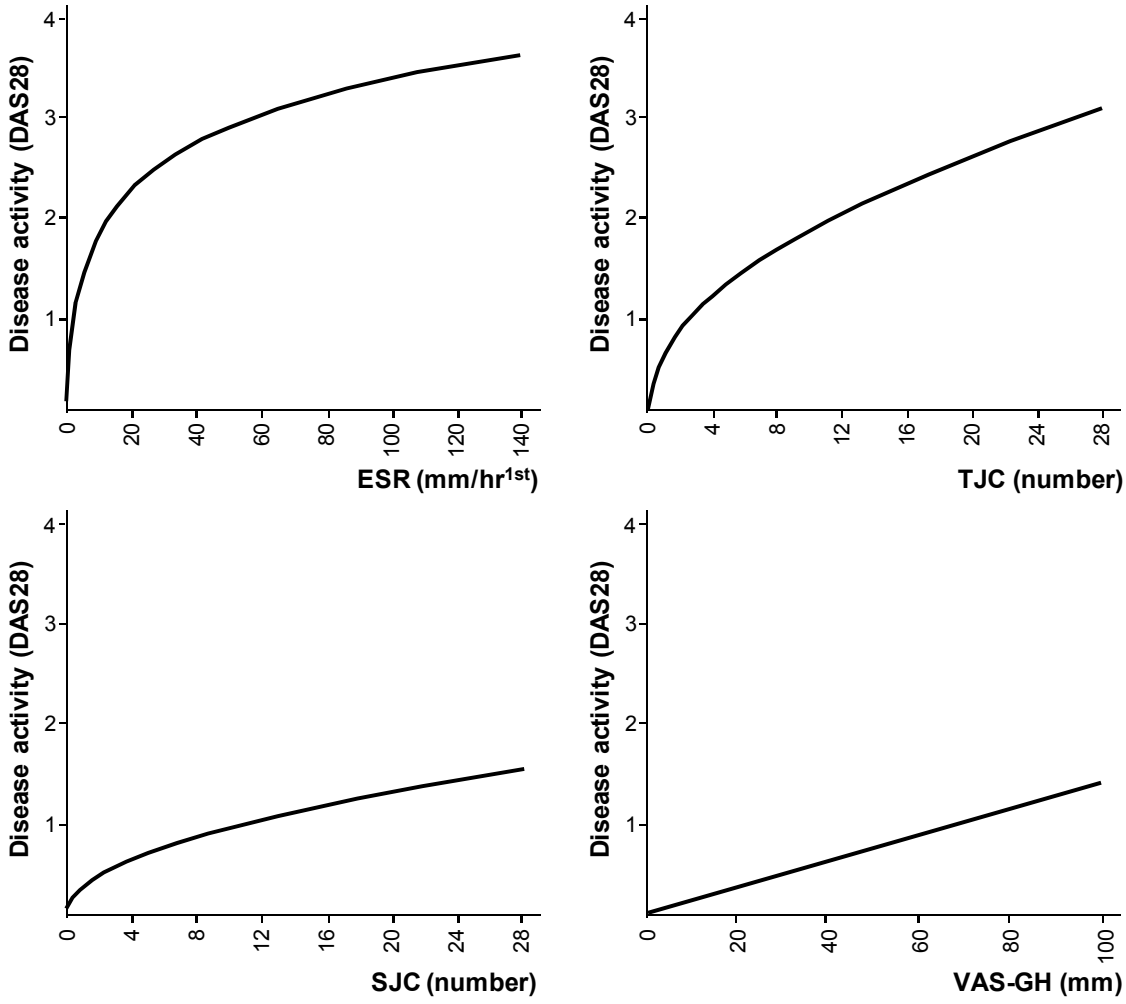


**Figure 1A-D.** Plots of contribution of individual components of DAS28 (X-axis) to the DAS28 score (Y-axis). For the X-axis of all figures the following calculations were used (determined with the DAS28 formula): ESR= 0.7*LN(X); TJC= 0.555*SQR(X); SJC= 0.284*SQR(X); VAS-GH= 0.0142*(X).
ESR= erythrocyte sedimentation rate; TJC= tender joint count; SJC= swollen joint count; VAS-GH= visual analogue scale for general well-being.

The DAS could lead to overestimation of disease activity in individual patients due to the DAS components TJS and VAS general well-being. Another problem for assessment of individual patients with RA is that the DAS28 does not include joints of the feet, which are frequently inflamed in RA. This could lead to underestimation of disease activity. The DAS28 remission criterion at a cut-off level of 2.6 has been found to lack construct validity for use in clinical practice for this reason.[37]

In our opinion, for the practical use of tight control, a new score should be developed and validated for the assessment in individuals, enabling comparison and pooling different study strategies. Probably the key criterion should be absence of swollen joints, because this is the key feature for RA. Further points of discussion are the duration of remission and whether radiographic progression should be included or not in remission criteria.

Overall, frequent monitoring on the basis of objective evidence of continued disease activity using a validated outcome measure and a quick, aggressive escalation protocol can improve the effects of RA considerably compared with routine care.[7, 38, 39] Other short-term and long-term advantages of tight control might be the greater improvement in physical function and substantially enhanced quality of life,[19] improved functional capacity,[31] decline of radiographic progression,[20, 22] and possible cost reductions for the future.[19] Disadvantages of tight control might be the frequency and intensity of the assessments, although the frequency might be high in early RA patients but less in established disease, and the fear of the patients for overtreatment due to the aggressive escalation protocol. The solution for overtreatment might be reduction of the medication in case of sustained response as applied in the BeSt and CAMERA study.

In conclusion, tight control seems to be a promising new paradigm for reaching the aim of low disease activity, or even better remission in clinical trials and possibly daily practice, due to a predefined decision and measurement system. For further implementation of this concept, development of a valid and easy to use criterion for remission is recommended.

## REFERENCES


1. Scott DL, Symmons DP, Coulton BL, et al. Long-term outcome of treating rheumatoid arthritis: results after 20 years. Lancet 1987;1:1108-11.
2. Pollard L, Choy EH, Scott DL. The consequences of rheumatoid arthritis: quality of life measures in the individual patient. Clin Exp Rheumatol 2005;23:S43-S52.
3. Raza K, Buckley CE, Salmon M, et al. Treating very early rheumatoid arthritis. Best Pract Res Clin Rheumatol 2006;20:849-63.
4. Boers M. Understanding the window of opportunity concept in early rheumatoid arthritis. Arthritis Rheum 2003;48:1771-4.
5. Moreland LW, Russell AS, Paulus HE. Management of rheumatoid arthritis: the historical context. J Rheumatol 2001;28:1431-52.
6. Wolfe F, Cush JJ, O'Dell JR, et al. Consensus recommendations for the assessment and treatment of rheumatoid arthritis. J Rheumatol 2001;28:1423-30.
7. Smolen JS, Aletaha D, Machold KP. Therapeutic strategies in early rheumatoid arthritis. Best Pract Res Clin Rheumatol 2005;19:163-77.
8. van der Heide A, Jacobs JW, Bijlsma JW, et al. The effectiveness of early treatment with "second-line" antirheumatic drugs. A randomized, controlled trial. Ann Intern Med 1996;124:699-707.
9. Capell HA, Madhok R, Porter DR, et al. Combination therapy with sulfasalazine and methotrexate is more effective than either drug alone in patients with rheumatoid arthritis with a suboptimal response to sulfasalazine: results from the double-blind placebo-controlled MASCOT study. Ann Rheum Dis 2007;66:235-41.
10. Landewe RB, Boers M, Verhoeven AC, et al. COBRA combination therapy in patients with early rheumatoid arthritis: long-term structural benefits of a brief intervention. Arthritis Rheum 2002;46:347-56.
11. Wilske KR, Healey LA. Remodeling the pyramid--a concept whose time has come. J Rheumatol 1989;16:565-7.
12. Bijlsma JW, Hoes JN, Van Everdingen AA, et al. Are glucocorticoids DMARDs? Ann.N.Y.Acad.Sci. 2006;1069:268-74.
13. Kirwan JR, Bijlsma JW, Boers M, et al. Effects of glucocorticoids on radiological progression in rheumatoid arthritis. Cochrane.Database.Syst.Rev. 2007:CD006356.
14. van der Heijde D, Klareskog L, Rodriguez-Valverde V, et al. Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. Arthritis Rheum 2006;54:1063-74.
15. Fransen J, Moens HB, Speyer I, et al. Effectiveness of systematic monitoring of rheumatoid arthritis disease activity in daily practice: a multicentre, cluster randomised controlled trial. Ann Rheum Dis 2005;64:1294-8.
16. Svensson B, Schaufelberger C, Teleman A, et al. Remission and response to early treatment of RA assessed by the Disease Activity Score. BARFOT study group. Better Anti-rheumatic Farmacotherapy. Rheumatology (Oxford) 2000;39:1031-6.
17. Makinen H, Kautiainen H, Hannonen P, et al. Sustained remission and reduced radiographic progression with combination disease modifying antirheumatic drugs in early rheumatoid arthritis. J Rheumatol 2007;34:316-21.
18. Mottonen T, Hannonen P, Leirisalo-Repo M, et al. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. Lancet 1999;353:1568-73.
19. Grigor C, Capell H, Stirling A, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. Lancet 2004;364:263-9.
20. Allaart CF, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, et al. Aiming at low disease activity in rheumatoid arthritis with initial combination therapy or initial monotherapy strategies: the BeSt study. Clin Exp Rheumatol 2006;24:S077-S82.
21. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. Arthritis Rheum 2005;52:3381-90.

22. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, et al. Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial. Ann Intern Med 2007;146:406-15.
23. Verstappen SM, Jacobs JW, van der Veen MJ, et al. Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open label trial). Ann Rheum Dis 2007;66:1443-9.
24. 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.
25. Prevoo ML, van 't Hof MA, Kuper HH, et al. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38:44-8.
26. van Gestel AM, Prevoo ML, van 't Hof MA, et al. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism Criteria. Arthritis Rheum 1996;39:34-40.
27. van der Heijde DM, van 't Hof M, van Riel PL, et al. Development of a disease activity score based on judgment in clinical practice by rheumatologists. J Rheumatol 1993;20:579-81.
28. Mottonen T, Paimela L, Leirisalo-Repo M, et al. Only high disease activity and positive rheumatoid factor indicate poor prognosis in patients with early rheumatoid arthritis treated with "sawtooth" strategy. Ann Rheum Dis 1998;57:533-9.
29. Teir J, Gray J, Pendlebury A, et al. Outcome of patients with early rheumatoid arthritis over a two year period. Ann Rheum Dis 1999;58:323.
30. Combe B, Landewe R, Lukas C, et al. EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2007;66:34-45.
31. Mierau M, Schoels M, Gonda G, et al. Assessing remission in clinical practice. Rheumatology (Oxford) 2007;46:975-9.
32. Ranganath VK, Khanna D, Paulus HE. ACR remission criteria and response criteria. Clin Exp Rheumatol 2006;24:S014-S21.
33. Molenaar ET, Voskuyl AE, Dinant HJ, et al. Progression of radiologic damage in patients with rheumatoid arthritis in clinical remission. Arthritis Rheum 2004;50:36-42.
34. Smolen JS, Aletaha D. What should be our treatment goal in rheumatoid arthritis today? Clin Exp Rheumatol 2006;24:S007-S13.
35. Makinen H, Hannonen P, Sokka T. Definitions of remission for rheumatoid arthritis and review of selected clinical cohorts and randomised clinical trials for the rate of remission. Clin Exp Rheumatol 2006;24:S022-S8.
36. van der Heijde DM, Jacobs JW. The original "DAS" and the "DAS28" are not interchangeable: comment on the articles by Prevoo et al. Arthritis Rheum 1998;41:942-5.
37. Landewe R, van der Heijde D, van der Linden S, et al. Twenty-eight-joint counts invalidate the DAS28 remission definition owing to the omission of the lower extremity joints: a comparison with the original DAS remission. Ann Rheum Dis 2006;65:637-41.
38. Emery P. Treatment of rheumatoid arthritis. BMJ 2006;332:152-5.
39. Zeidler H, Hulsemann JL. How should best strategy and tight control be translated into clinical practice? Comment on the article by Goekoop-Ruiterman et al. Arthritis Rheum 2006;54:2338-9.

Chapter 3

# Adverse events and factors associated with toxicity in patients with early rheumatoid arthritis treated with methotrexate tight control therapy: the CAMERA study

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## ABSTRACT

### Objective

To evaluate toxicity profiles in patients with early rheumatoid (RA) treated either according to an intensive treatment strategy approach or to a conventional treatment strategy approach with methotrexate (MTX) and to study factors associated with MTX related toxicity.

### Methods

Data of 289 patients with early RA were used from the CAMERA study in which clinical efficacy of an intensive treatment strategy with MTX was more beneficial than a conventional treatment strategy approach. In the present study, data on adverse events (AEs) were compared between the two strategy groups. Logistic regression analyses were used to identify possible associations between demographic, clinical and laboratory factors assessed at baseline and withdrawal due to MTX related AEs or liver toxicity at follow-up.

### Results

Although significantly more patients in the intensive strategy group experienced MTX related AEs than in the conventional strategy group, all recorded AEs were relatively mild. A higher body mass index (BMI) was significantly associated with withdrawal due to MTX related AEs in the multiple regression analyses (OR=1.207, 95%CI 1.02-1.44, p=0.033). There was a trend towards an association between diminished creatinine clearance and MTX withdrawal. For liver toxicity, increased serum liver enzymes at baseline were associated with liver toxicity during follow-up.

### Conclusion

Although the occurrence of AEs in the intensive strategy group was higher than in the conventional strategy group, the previously observed clinical efficacy of an intensive treatment strategy seems to outweigh the observed toxicity profiles. When starting MTX, attention should be given to patients with a high BMI and those with increased levels of liver enzymes and decreased renal function.

## INTRODUCTION

Methotrexate (MTX) is usually selected as initial treatment and as anchor drug in combination therapies for rheumatoid arthritis (RA), because of its proven effectiveness as single drug and in combination therapy, wide dose range, and relatively mild toxicity profile.[1-3] Compared to other conventional disease modifying anti-rheumatic drugs (DMARDs), MTX is general used for a longer period of time.[4-6] Discontinuation of MTX is more likely to be due to manifestations of adverse events (AEs) than because of inefficacy.[7,8]
Frequently observed AEs of MTX include hepatotoxicity and gastrointestinal (GI) problems; pulmonary toxicity and pancytopenia rarely occur. The use of folic acid has decreased the occurrence of adverse effects, especially hepatotoxicity and GI adverse effects.
In studies older age,[9] younger age,[10] duration of MTX treatment,[9] dose of MTX,[11] female gender,[10,11] high body mass index (BMI),[10-12] renal impairment,[13] increased liver enzyme levels,[11] functional disability,[14] and no concomitant use of folic acid [10,12] were identified as possible predictors of liver toxicity or other AEs. However, the results of these randomized clinical trials, often lacking specific data on AEs, and retrospective observational studies, were not always consistent. Retrospective observational studies have the advantage of being representative for routine practice, but have the drawback that desirable data such as possible predictors and description of AEs may be missing.
In the 2-year Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA) study,[15] more patients in the intensive MTX strategy group (TC strategy group) than in the conventional MTX strategy group (CT strategy group) achieved at least one period of remission during follow-up. However, to compare the value of the two strategies, it is important to weigh both beneficial effects and adverse effects.
The aim of the present study was to compare a broad spectrum of toxicity profiles between both MTX treatment strategies and to study possible associations between baseline characteristics with MTX related withdrawal and liver toxicity during follow-up.

## PATIENTS AND METHODS

From 1999 to 2003, all early RA patients (disease duration <1 year) who fulfilled the 1987 revised American College of Rheumatology (ACR) criteria for RA [16] were asked to participate in the two-year randomized, open-label prospective multi-centre CAMERA trial. Patients visited the outpatient clinic of one of the six rheumatology departments in the region of Utrecht, the Netherlands, collaborating in the Utrecht Rheumatoid Arthritis Cohort study group. Exclusion criteria included a creatinine clearance of <75 ml/min, serum aspartate aminotransferase (AST) or serum alanine aminotransferase (ALT) more than twice the upper limit of normal (ULN) and alcohol intake of >2 units a day. The study population in this study included all patients who used MTX for at least 1 week. Medical ethical committees of all participating hospitals approved this study, and all patients gave written informed consent before entering the study.

**Treatment**

Patients were randomly allocated to either the TC strategy or the CT strategy. Patients in the TC strategy came to the outpatient clinic once every 4 weeks and patients in the CT strategy once every 3 months. In both groups, patients commenced on 7.5 mg/wk MTX and dosage MTX was not changed if, compared to the previous visit, patients had responded to treatment; otherwise the dosage was increased stepwise by 5 mg/wk until remission or a maximum of 30 mg/wk, if necessary. If the maximum oral dose MTX was reached, in case of insufficient response, MTX was administered subcutaneously (scMTX) (see reference [15] for response criteria). For patients on scMTX having an inadequate response, cyclosporine was added to the MTX therapy. If patients fulfilled the criteria for sustained response, MTX was stepwise reduced by 2.5 mg/wk as long as patients met these criteria; otherwise dose of MTX was continued or increased again according to the protocol. Folic acid (0.5 mg/day, except on the day of MTX was taken) was prescribed to every patient.

Criteria for dose adjustments, discontinuation of MTX and starting of cyclosporine as a consequence of AEs were dictated by the study protocol. For liver toxicity, these criteria were based on guidelines for monitoring liver toxicity.[17] Number of leucocytes between 2.5 and $3.5x10^9$/l, number of thrombocytes between 100 and $150x10^9$/l, mouth ulcers, or a 25% decrease in creatinine clearance was considered a cause for withholding MTX until these values returned to normal or mouth ulcers disappeared. Leucocytes count of $\leq 2.5x10^9$/l, thrombocyte count of $\leq 100x10^9$/l, or pneumonitis were considered reasons for discontinuation of MTX and start of cyclosporine. scMTX was considered following severe nausea or dyspepsia. Possible adaptations in MTX therapy in case of anaemia were made by the rheumatologist.

**Assessment and definitions**

In both strategy groups, AEs were recorded at every visit using a predefined form, categorized into GI, mucocutaneous, central nervous system (CNS), liver toxicity, renal, hematological, pulmonary disorders, infections, general AEs, post-dosing reactions, and “other” AEs. Creatinine increase was defined as an increase of >20 µmol/l compared with the previous protocol visit and heamatological AEs included anaemia (Hb <6.5 mmol/l), leucopenia ($<3.5x10^9$/l), thrombocytopenia ($<150x10^9$/l), or pancytopenia (two out of three of these criteria). Patients with normal blood pressure values at baseline were defined as hypertensive at follow-up using World Health Organization (WHO) thresholds.[18] Based on normal values of the individual laboratories of participating centres, liver toxicity was defined as a value for AST or ALT greater than ULN.

**Statistical analyses**

*Withdrawals*

Logistic regression analysis was used to determine the association between strategy groups and withdrawal due to MTX and/or cyclosporine related AEs. In the total study population, possible baseline predictors of withdrawal due to AEs were identified applying simple and

multiple logistic regression analyses. Both unadjusted and adjusted (for the strategy arm and baseline nonsteroidal anti-inflammatory drug (NSAID) use) odds ratios (ORs) with 95% confidence intervals (CI) are presented. In the multiple regression analyses, the variables which were significant in simple analyses and known possible predictors for MTX related AEs (BMI, Health Assessment Questionnaire (HAQ), creatinine clearance, ALT) were included in the model.

*Adverse events*
For the TC strategy and the CT strategy separately, the number of patients with an AE and the total number of AEs are described. Comparison of percentages of patients with an AE was carried out using the Fisher exact test. We also expressed the number of events per number of evaluations because of differences in frequency of study visits between the two strategy groups.
Changes in creatinine clearance over 2 years between the two strategy groups, adjusted for NSAID and cyclosporine use during follow-up, were tested using multiple linear regression. For the seven main categories of AEs, the cumulative dose of MTX and dose of MTX in the month before the first recorded AE were compared between the two strategy groups using t-tests or Mann Whitney-U tests, depending on the distribution of the data.

*Liver toxicity*
Within each treatment strategy group, the cumulative dose of MTX over 2 years was compared between completers with liver toxicity versus those without liver toxicity. For the TC strategy and CT strategy separately, multiple logistic regression analyses were used to assess the association between possible baseline predictors and liver toxicity (i.e. AST and/or ALT >ULN) at follow-up. Since patients with liver enzyme levels up to twice the ULN were included in the study, we subsequently performed the same analyses including only those patients with liver enzyme levels <ULN at baseline. ORs were adjusted for NSAID use at baseline. All analyses were performed using SPSS version 15.0.

## RESULTS

The total study population consisted of 289 patients, 149 in the TC strategy group and 140 in the CT strategy. Table 1 shows the baseline patient characteristics, reasons for withdrawal and number of patients using cyclosporine during follow-up. Mean (SD) age of the total study population was 53 (15) years; 193/289 (67%) patients were female and 168/258 (65%) patients were RF positive. At baseline, NSAIDs were taken by 116 (78%) patients in the TC strategy and 110 (79%) patients in the CT strategy. Cyclosporine was prescribed to 39/149 (26%) patients in the TC strategy and 7/140 (5%) patients in the CT strategy during the study.

| Variables | TC strategy n | TC strategy value | CT strategy n | CT strategy value |
|---|---|---|---|---|
| Demographic variables (mean(SD)) | | | | |
| Age (years) | 149 | 54 (14) | 140 | 52 (15) |
| Gender (% female) | 149 | 68.5 | 140 | 65.0 |
| BMI (kg/m$^2$) | 107 | 25 (4) | 104 | 26 (4) |
| Clinical variables (mean(SD)) | | | | |
| SJC (number) | 149 | 14 (6) | 138 | 14 (6) |
| TJC (number) | 148 | 15 (7) | 137 | 14 (7) |
| VAS pain (mm) | 143 | 53 (26) | 135 | 47 (25) |
| VAS general well-being (mm) | 146 | 54 (22) | 135 | 52 (22) |
| Functional disability (HAQ) | 119 | 1.30 (0.7) | 109 | 1.25 (0.7) |
| Labaratory values (mean(SD)) | | | | |
| ESR (mm/hr$^{1st}$) | 148 | 37 (27) | 138 | 39 (25) |
| Male | 47 | 31 (27) | 48 | 36 (26) |
| Female | 101 | 40 (27) | 90 | 40 (24) |
| Hb (mmol/l) | 148 | 8.0 (0.8) | 140 | 8.0 (0.8) |
| Male | 47 | 8.6 (0.7) | 49 | 8.5 (0.7) |
| Female | 101 | 7.8 (0.7) | 91 | 7.7 (0.7) |
| Creatinine (µmol/l) | 146 | 74 (14) | 138 | 73 (13) |
| Male | 46 | 84 (11) | 49 | 83 (12) |
| Female | 100 | 70 (12) | 89 | 68 (11) |
| Creatinine clearance (ml/min) | 136 | 98 (27) | 131 | 101 (28) |
| Male | 43 | 103 (30) | 44 | 111 (26) |
| Female | 93 | 95 (26) | 87 | 96 (28) |
| AST (U/L) | 145 | 23 (8) | 135 | 23 (8) |
| Male | 45 | 24 (7) | 48 | 24 (8) |
| Female | 100 | 23 (8) | 87 | 23 (8) |
| ALT (U/L) | 147 | 22 (13) | 139 | 21 (12) |
| Male | 46 | 25 (12) | 49 | 21 (9) |
| Female | 101 | 21 (13) | 90 | 20 (13) |
| RF (% positive) | 134 | 66.4 | 124 | 63.7 |
| Medical history (n) | | | | |
| Diabetes mellitus | 4 | | 4 | |
| Hypertension | 69 | | 67 | |
| Grade 1 | 40 | | 36 | |
| Grade 2 | 18 | | 22 | |
| Grade 3 | 11 | | 9 | |
| Cardiovascular disease | 7 | | 10 | |
| COPD | 6 | | 6 | |
| Reasons for withdrawal (n) | | | | |
| MTX toxicity | 16 | | 8 | |
| Cyclosporine toxicity | 10 | | 1 | |
| Loss of efficacy | 13 | | 4 | |
| Other or unknown | 18 | | 14 | |
| Cyclosporine use during follow-up (n) | 39 | | 7 | |
| NSAID use at baseline (n) | 116 | | 110 | |

**Table 1** Characteristics at start of the study and reasons for withdrawal during the study.
Values are mean (SD) or percentages. TC strategy= intensive treatment strategy group; CT strategy= conventional treatment strategy group; n= number of patients with available data; BMI= body mass index; SJC= swollen joint count; TJC= tender joint count; VAS= visual analogue scale (range 0-100 mm, worst score); HAQ= Health Assessment Questionnaire (0-3, most functional disability); ESR= erythrocyte sedimentation rate; Hb= haemoglobin; AST= serum aspartate aminotransferase; ALT= serum alanine aminotransferase; COPD= chronic obstructive pulmonary disease; MTX= methotrexate; NSAID= nonsteroidal anti-inflammatory drug.

**Withdrawals**

In total, 16/149 (11%) patients in the TC strategy and 8/140 (6%) patients in the CT strategy withdrew because of MTX related AEs including, respectively: liver toxicity (n=6 vs. n=1), increased serum creatinine (n=1 vs. n=0), pulmonary disorders (n=2 vs. n=2), and other AEs such as nausea or oral ulcers (n=7 vs. n=5). After the start of cyclosporine, 11 patients withdrew because of different AEs, including hypertension (n=2) (Table 1).

There was no association between the strategy group and withdrawal due to MTX related AEs (OR=1.985, 95%CI 0.82-4.80, p=0.128), but patients in the TC strategy were more likely to withdraw due to MTX and/or cyclosporine related AEs (OR=3.080, 95%CI 1.39-6.83, p=0.006).

None of the baseline variables was associated with withdrawal due to MTX related AEs in the univariate regression analyses (Table 2).

| Variables | **Unadjusted OR (95%CI)** | **p** | **Adjusted OR (95%CI)** | **p** |
|---|---|---|---|---|
| Age (years) | 1.001 (0.97-1.03) | 0.961 | 0.997 (0.97-1.03) | 0.842 |
| Gender (female vs. male) | 1.228 (0.49-3.07) | 0.660 | 1.250 (0.49-3.17) | 0.639 |
| BMI (kg/m$^2$) | 1.074 (0.96-1.20) | 0.197 | 1.076 (0.95-1.21) | 0.236 |
| SJC (number) | 0.956 (0.89-1.03) | 0.250 | 0.956 (0.89-1.03) | 0.250 |
| TJC (number) | 0.991 (0.93-1.06) | 0.779 | 0.986 (0.93-1.05) | 0.677 |
| VAS pain (mm) | 1.012 (1.00-1.03) | 0.172 | 1.007 (0.99-1.03) | 0.398 |
| VAS general well-being (mm) | 1.011 (0.99-1.03) | 0.247 | 1.010 (0.99-1.03) | 0.327 |
| Functional disability (HAQ) | 1.316 (0.66-2.62) | 0.433 | 1.138 (0.54-2.38) | 0.732 |
| ESR (mm/hr$^{1st}$) | 0.987 (0.97-1.01) | 0.191 | 0.987 (0.97-1.01) | 0.193 |
| Creatinine (µmol/l) | 1.013 (0.98-1.05) | 0.444 | 1.008 (0.98-1.04) | 0.644 |
| Creatinine clearance (ml/min) | 0.999 (0.98-1.02) | 0.953 | 1.002 (0.98-1.02) | 0.872 |
| AST (U/L) | 0.992 (0.94-1.05) | 0.765 | 0.992 (0.94-1.05) | 0.761 |
| ALT (U/L) | 1.008 (0.98-1.04) | 0.607 | 0.999 (0.97-1.03) | 0.959 |
| RF (positive vs. negative) | 2.263 (0.73-6.99) | 0.156 | 2.464 (0.77-7.89) | 0.129 |

**Table 2** Association between baseline demographic characteristics, clinical data and laboratory values with MTX related adverse events.

Unadjusted and adjusted odds ratios (OR) (adjusted for treatment strategy and NSAID use at baseline). 95%CI= 95% confidence interval; BMI= body mass index; SJC= swollen joint count; TJC= tender joint count; VAS= visual analogue scale (range 0-100 mm, worst score); HAQ= Health Assessment Questionnaire (0-3, most functional disability); ESR= erythrocyte sedimentation rate; AST= serum alanine aminotransferase; ALT= serum aspartate aminotransferase; RF= rheumatoid factor.

Data of 167 patients were available for the multiple regression analyses. In the final model, increased BMI (OR=1.207, 95%CI 1.02-1.44, p=0.033) and a trend towards decreased creatinine clearance (OR=0.974, 95%CI 0.94-1.00, p=0.093) were associated with withdrawal due to MTX related AEs. More pain at baseline (unadjusted OR=1.016, 95%CI 1.00-1.03, p=0.042 and adjusted OR=1.011, 95%CI 1.00-1.03, p=0.149) and increased ALT levels (unadjusted OR=1.027, 95%CI 1.00-1.05, p=0.033 and adjusted OR=1.020, 95%CI 0.99-1.05, p=0.134) were associated with withdrawal of patients experiencing any treatment

(MTX and/or cyclosporine) related AEs in the univariate regression analyses, but not in the multivariate regression analyses (data not shown).

**Adverse events**

AEs were reported for 268 patients; 142/149 (95%) patients in the TC strategy and 126/140 (90%) patients in the CT strategy. For the seven main categories of AEs, the percentages of patients with an event were respectively: GI symptoms (66% vs. 54%, p=0.030); mucocutaneous (54% vs. 40%, p=0.025); CNS (59% vs. 39%, p=0.001); hepatic (55% vs. 35%, p=0.001); renal (39% vs. 44%, p=0.403); haematological (26% vs. 11%, p=0.001), and general AEs (27% vs. 15%, p=0.0151).

The reported AEs were mostly mild; frequently reported symptoms were nausea, oral ulcers, dizziness, headache, fatigue, and stomach ache (see Table 3).

Fifteen percent of the patients with headaches and 19% of the patients in whom creatinine levels increased during follow-up had received cyclosporine before the AE. Of patients with a normal blood pressure at baseline, 27 patients were hypertensive at follow-up. That is, WHO hypertension grade 2 and/or grade 3. Five of these patients had received cyclosporine.

After 2 years, creatinine clearance had significantly decreased from baseline; mean decrease in the TC strategy (n=70) was 7.7 ml/min (95%CI 4.7-10.7, p<0.001) and 7.8 ml/min (95%CI 4.9-10.7, p<0.001) in the CT strategy (n=95). These changes were not statistically different between the two strategy groups (estimated difference -0.46, 95%CI -4.8-3.9). One patient in the TC strategy and three patients in the CT strategy had reversible pancytopenia. Seven patients, four in the TC strategy and three in the CT strategy, experienced relatively severe pulmonary disorders (e.g. pleuritis, restrictive lung disease and exacerbation of chronic obstructive pulmonary disease), but none of the patients developed pneumonia or pneumonitis. Three (43%) of these patients already had lung disorders before entry into the study.

Except for haematological AEs, the dose of MTX before the first recorded event was significantly higher for the TC strategy than for the CT strategy (Table 4). However, the median cumulative dose of MTX until the first recorded event was, except for GI AEs, similar between the two strategy groups.

**Liver toxicity**

Of patients with available AST and ALT levels at one year, respectively 10/122 (8.2%) and 16/124 (12.9%) in the TC strategy and 11/126 (8.7%) and 15/128 (11.7%) in the CT strategy had an increase >ULN (AST and ALT; ns). At two years, these numbers were 3/88 (3.4%) and 5/89 (5.6%) in the TC strategy and 5/109 (4.6%) and 8/111 (7.2%) in the CT strategy (AST and ALT; ns).

| | TC strategy | | | | | CT strategy | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n with AE | AE/evaluations | severity AE* | | | n with AE | AE/evaluations | severity AE* | | |
| Variables | | | mild | moderate | severe | | | mild | moderate | severe |
| GI symptoms | 99 (66.4) | 576/3191 (18.1) | | | | 75 (53.6) | 215/1132 (19.0) | | | |
| Nausea | 76 (51.0) | 309/3191 (9.7) | 81 (68) | 33 (27) | 6 (5) | 47 (33.6) | 108/1132 (9.5) | 27 (64) | 12 (29) | 3 (7) |
| Vomiting | 14 (9.4) | 18/3191 (0.6) | 4 (67) | 2 (33) | 0 (0) | 6 (4.3) | 9/1132 (0.8) | 2 (50) | 1 (25) | 1 (25) |
| Anorexia | 4 (2.7) | 5/3191 (0.2) | 2 (40) | 3 (60) | 0 (0) | 1 (0.7) | 2/1132 (0.2) | | | |
| Stomach ache | 35 (23.5) | 79/3191 (2.5) | 13 (46) | 11 (40) | 4 (14) | 13 (9.3) | 18/1132 (1.6) | 4 (67) | 2 (33) | 0 (0) |
| Diarrhoea | 21 (14.1) | 41/3191 (1.3) | 11 (48) | 9 (39) | 3 (13) | 17 (12.1) | 30/1132 (2.7) | 9 (69) | 42 (31) | 0 (0) |
| Other | 53 (35.6) | 124/3191 (3.9) | 14 (61) | 8 (35) | 1 (4) | 32 (22.9) | 48/1132 (4.2) | 16 (70) | 7 (30) | 0 (0) |
| GI findings | 3 (2.0) | 7/3191 (0.2) | | | | 1 (0.7) | 2/1132 (0.2) | | | |
| Oesophagitis | 1 (0.7) | 5/3191 (0.2) | 1 (50) | 1 (50) | 0 (0) | 1 (0.7) | 2/1132 (0.2) | 0 (0) | 1 (100) | 0 (0) |
| Gastritis | 0 | | | | | 0 | | | | |
| Gastric ulcers | 0 | | | | | 0 | | | | |
| Duodenal ulcers | 0 | | | | | 0 | | | | |
| Colitis | 0 | | | | | 0 | | | | |
| Other | 2 (1.3) | 2/3191 (0.1) | 1 (100) | 0 (0) | 0 (0) | 0 | | | | |
| Mucocutaneous | 80 (53.7) | 373/3191 (11.7) | | | | 56 (40.0) | 161/1132 (14.2) | | | |
| Nodulosis | 4 (2.7) | 4/3191 (0.1) | 0 (0) | 1 (100) | 0 (0) | 2 (1.4) | 2/1132 (0.2) | 1 (100) | 0 (0) | 0 (0) |
| Stomatitis | 12 (8.1) | 18/3191 (0.6) | 7 (78) | 1 (11) | 1 (11) | 8 (5.7) | 9/1132 (0.8) | 2 (50) | 1 (25) | 1 (25) |
| Oral ulcers | 41 (27.5) | 85/3191 (2.7) | 31 (83) | 5 (14) | 1 (3) | 25 (17.9) | 49/1132 (4.3) | 10 (62) | 6 (38) | 0 (0) |
| Itching | 23 (15.4) | 42/3191 (1.3) | 12 (86) | 2 (14) | 0 (0) | 19 (13.6) | 25/1132 (2.2) | 4 (67) | 1 (33) | 0 (0) |
| Alopecia | 17 (11.4) | 79/3191 (2.5) | 26 (65) | 14 (35) | 0 (0) | 15 (10.7) | 28/1132 (2.5) | 8 (73) | 3 (27) | 0 (0) |
| Hypertrichosis | 3 (2.0) | 9/3191 (0.3) | 2 (67) | 1 (33) | 0 (0) | 1 (0.7) | 1/1132 (0.1) | 0 (0) | 1 (100) | 0 (0) |
| Gum hyperplasia | 13 (8.7) | 28/3191 (0.9) | 8 (62) | 5 (38) | 0 (0) | 3 (2.1) | 3/1132 (0.3) | 2 (100) | 0 (0) | 0 (0) |
| Other | 47 (31.5) | 108/3191 (3.4) | 13 (56) | 8 (35) | 2 (9) | 24 (17.1) | 44/1132 (3.9) | 5 (56) | 2 (22) | 2 (22) |
| CNS | 88 (59.1) | 453/3191 (14.2) | | | | 54 (38.6) | 169/1132 (14.9) | | | |
| Headache | 44 (29.5) | 117/3191 (3.7) | 18 (57) | 11 (34) | 3 (9) | 17 (12.1) | 31/1132 (2.7) | 10 (91) | 1 (9) | 0 (0) |
| Dizziness | 36 (24.2) | 85/3191 (2.7) | 18 (69) | 7 (27) | 1 (4) | 24 (17.1) | 49/1132 (4.3) | 12 (67) | 6 (33) | 0 (0) |
| Disordered mood | 19 (12.8) | 42/3191 (1.3) | 5 (50) | 5 (50) | 0 (0) | 11 (7.9) | 23/1132 (2.0) | 2 (33) | 4 (67) | 0 (0) |
| Blurred vision | 17 (11.4) | 40/3191 (1.3) | 5 (83) | 1 (17) | 0 (0) | 9 (6.4) | 16/1132 (1.4) | 0 (0) | 2 (100) | 0 (0) |
| Dry eyes | 17 (11.4) | 51/3191 (1.6) | 11 (58) | 5 (26) | 3 (16) | 6 (4.3) | 6/1132 (0.5) | 2 (100) | 0 (0) | 0 (0) |
| Lost hearing | 4 (2.7) | 5/3191 (0.2) | | | | 4 (2.9) | 5/1132 (0.4) | 1 (50) | 1 (50) | 0 (0) |
| Other | 52 (34.9) | 113/3191 (3.5) | 16 (44) | 19 (51) | 2 (5) | 22 (15.7) | 39/1132 (3.5) | 7 (59) | 4 (33) | 1 (8) |

**Table 3** Overview of number of patients with an adverse event and frequency of adverse events corrected for total number of evaluated visits - continued.

| Variables | TC strategy n with AE | TC strategy AE/evaluations | TC strategy severity AE* mild | TC strategy severity AE* moderate | TC strategy severity AE* severe | CT strategy n with AE | CT strategy AE/evaluations | CT strategy severity AE* mild | CT strategy severity AE* moderate | CT strategy severity AE* severe |
|---|---|---|---|---|---|---|---|---|---|---|
| Renal | 58 (38.9) | 326/3191 (10.2) | | | | 62 (44.3) | 178/1132 (15.7) | | | |
| Proteinuria | 0 | | | | | 0 | | | | |
| Elevated serum creatinine | 19 (12.8) | 32/2935 (1.1) | | | | 23 (16.4) | 23/1066 (2.2) | | | |
| Hypertension | 44 (29.5) | 287/2391 (12.0) | | | | 43 (30.7) | 115/904 (17.2) | | | |
| Increased potassium | 1 (0.7) | 1/3191 (0.03) | | | | 0 | | | | |
| Increased uric acid | 0 | | | | | 0 | | | | |
| Other | 3 (2.0) | 6/3191 (0.2) | | | | 0 | | | | |
| Hepatic | 82 (55.0) | 550/3191 (17.2) | | | | 49 (35.0) | 163/1132 (14.4) | | | |
| ALT | 70 (47.0) | 335/3128 (10.7) | | | | 40 (29.0) | 102/1107 (9.2) | | | |
| 1-2 * ULN | 41 | | | | | 32 | | | | |
| 2-3 * ULN | 15 | | | | | 5 | | | | |
| >3 * ULN | 14 | | | | | 3 | | | | |
| AST | 63 (42.3) | 208/2996 (6.9) | | | | 30 (21.4) | 61/1049 (5.8) | | | |
| 1-2 * ULN | 48 | | | | | 23 | | | | |
| 2-3 * ULN | 15 | | | | | 6 | | | | |
| >3 * ULN | 0 | | | | | 1 | | | | |
| Alkaline phosphatase | 2 (1.3) | 2/3191 (10.2) | | | | 0 | | | | |
| Gamma-GGT | 3 (2.0) | 5/3191 (0.2) | | | | 0 | | | | |
| Other | 0 | | | | | 0 | | | | |
| Haematological | 38 (25.5) | 178/3191 (5.6) | | | | 15 (10.7) | 38/1132 (3.4) | | | |
| Anaemia | 19 (12.8) | 41/3140 (1.3) | | | | 10 (7.1) | 18/1113 (1.6) | | | |
| Leucopenia | 4 (2.7) | 5/3122 (0.2) | | | | 3 (2.1) | 8/1110 (0.7) | | | |
| Thrombocytopenia | 14 (9.4) | 120/3102 (3.9) | | | | 5 (3.6) | 8/1109 (0.7) | | | |
| Pancytopenia | 1 (0.7) | 1/3102 (0.03) | | | | 3 (2.1) | 3/1109 (0.3) | | | |
| Other | 4 (2.7) | 11/3102 (0.4) | | | | 1 (0.7) | 1/1109 (0.1) | | | |
| Lung symptoms | 21 (14.1) | 44/3191 (1.4) | | | | 19 (13.6) | 33/1132 (2.9) | | | |
| Cough | 15 (10.1) | 30/3191 (0.9) | 7 (54) | 6 (46) | 0 (0) | 12 (8.6) | 19/1132 (1.7) | 2 (40) | 2 (40) | 1 (20) |
| Dyspnoea | 8 (5.4) | 11/3191 (0.3) | 2 (50) | 1 (25) | 1 (25) | 1 (0.7) | 2/1132 (0.2) | 1 (100) | 0 (0) | 0 (0) |
| Chest pain | 1 (0.7) | 1/3191 (0.03) | | | | 0 | | | | |
| Other | 2 (1.3) | 2/3191 (0.06) | | | | 10 (7.1) | 12/1132 (1.1) | 2 (67) | 1 (33) | 0 (0) |

**Table 3** Overview of number of patients with an adverse event and frequency of adverse events corrected for total number of evaluated visits - continued.

| | TC strategy | | | | | CT strategy | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n with AE | AE/evaluations | severity AE* | | | n with AE | AE/evaluations | severity AE* | | |
| Variables | | | mild | moderate | severe | | | mild | moderate | severe |
| Lung findings | 4 (2.7) | 4/3191 (0.1) | | | | 3 (2.1) | 3/1132 (0.3) | | | |
| Pneumonitis/pneumonia | 0 | | | | | 0 | | | | |
| Other | 4 (2.7) | 4/3191 (0.1) | | | | 3 (2.1) | 3/1132 (0.3) | | | |
| General | 40 (26.9) | 73/3191 (2.3) | | | | 21 (15.0) | 31/1132 (2.7) | | | |
| Fever | 5 (3.4) | 6/3191 (0.2) | 2 (67) | 1 (33) | 0 (0) | 3 (2.1) | 3/1132 (0.3) | 1 (50) | 0 (0) | 1 (50) |
| Weight loss | 1 (0.7) | 1/3191 (0.2) | | | | 2 (1.4) | 4/1132 (0.4) | 1 (100) | 0 (0) | 0 (0) |
| Fatigue | 34 (22.8) | 60/3191 (1.9) | 7 (41) | 9 (53) | 1 (6) | 14 (10.0) | 22/1132 (1.9) | 2 (50) | 2 (50) | 0 (0) |
| Other | 5 (3.4) | 6/3191 (0.2) | | | | 2 (1.4) | 2/1132 (0.2) | 2 (100) | 0 (0) | 0 (0) |
| Post dosing reactions | 19 (12.8) | 42/3191 (1.3) | | | | 8 (5.7) | 17/1132 (1.5) | | | |
| Arthralgia | 9 (6.0) | 17/3191 (0.5) | 7 (70) | 1 (10) | 2 (20) | 5 (3.6) | 6/1132 (0.5) | 0 (0) | 2 (100) | 0 (0) |
| Stiffness | 10 (6.7) | 14/3191 (0.4) | 3 (42) | 2 (29) | 2 (29) | 6 (4.3) | 9/1132 (0.8) | 1 (33) | 2 (67) | 0 (0) |
| Other | 10 (6.7) | 11/3191 (0.3) | 1 (33) | 1 (33) | 1 (33) | 2 (1.4) | 2/1132 (0.2) | 2 (100) | 0 (0) | 0 (0) |
| Other | 19 (12.8) | 34/3191 (1.1) | | | | 6 (4.3) | 6/1132 (0.5) | | | |
| Other | 19 (12.8) | 28/3191 (0.9) | 5 (42) | 6 50) | 1 (8) | 6 (4.3) | 6/1132 (0.5) | 2 (100) | 0 (0) | 0 (0) |
| Cardiovascular | 4 (2.7) | 6/3191 (0.2) | 2 (100) | 0 (0) | 0 (0) | 0 | | | | |

**Table 3** Overview of number of patients with an adverse event and frequency of adverse events corrected for total number of evaluated visits.
Values are n (%) or n/total observations (%).
* Severity of adverse event according to rheumatologist. Since the rheumatologist could optionally describe the severity of an adverse event, the sum of the three coding for severity (i.e. mild, moderate, severe) is less than the total number of reported adverse events.
TC strategy= intensive treatment strategy group, CT strategy= conventional strategy group; AE= adverse event; GI= gastrointestinal; CNS= central nervous system; ALT= serum aspartate aminotransferase; AST= serum alanine aminotransferase; ULN= upper limit of normal.

| Variables | n TC | n CT | cum dose of MTX until first event TC mean (SD) | median | CT mean (SD) | median | p | dose of MTX before first event TC mean (SD) | CT mean (SD) | p |
|---|---|---|---|---|---|---|---|---|---|---|
| GI symptoms | | | | | | | | | | |
| All patients | 99 | 75 | 400 (479) | 185 | 504 (495) | 330 | 0.406 | 16.6 (7.3) | 13.3 (6.1) | 0.002 |
| Completers | 62 | 62 | 434 (538) | 188 | 547 (524) | 343 | 0.051 | 16.3 (7.1) | 13.8 (6.2) | 0.039 |
| Mucocutaneous | | | | | | | | | | |
| All patients | 80 | 56 | 589 (631) | 362 | 508 (548) | 275 | 0.870 | 17.7 (7.9) | 13.6 (7.5) | 0.003 |
| Completers | 50 | 45 | 592 (648) | 343 | 551 (578) | 286 | 0.800 | 18.3 (8.4) | 14.4 (7.8) | 0.022 |
| CNS | | | | | | | | | | |
| All patients | 88 | 54 | 647 (676) | 345 | 507 (547) | 282 | 0.911 | 16.5 (8.0) | 12.3 (5.6) | <0.001 |
| Completers | 53 | 44 | 773 (722) | 530 | 563 (588) | 312 | 0.341 | 17.5 (7.9) | 12.4 (5.4) | <0.001 |
| Renal | | | | | | | | | | |
| All patients | 58 | 62 | 509 (545) | 267 | 449 (461) | 266 | 0.759 | 15.7 (8.3) | 12.0 (5.2) | 0.004 |
| Completers | 39 | 51 | 590 (592) | 281 | 504 (475) | 300 | 1.000 | 15.7 (8.1) | 12.6 (5.4) | 0.042 |
| Hepatic | | | | | | | | | | |
| All patients | 82 | 49 | 536 (513) | 299 | 668 (517) | 540 | 0.154 | 19.5 (7.5) | 14.8 (6.0) | <0.001 |
| Completers | 53 | 47 | 614 (571) | 413 | 662 (524) | 540 | 0.666 | 19.9 (7.5) | 14.7 (6.0) | <0.001 |
| Haematological | | | | | | | | | | |
| All patients | 38 | 15 | 618 (686) | 284 | 600 (589) | 315 | 0.643 | 15.4 (8.5) | 14.3 (6.7) | 0.667 |
| Completers | 25 | 14 | 758 (752) | 393 | 636 (593) | 406 | 0.897 | 16.2 (8.5) | 14.8 (6.7) | 0.604 |
| General | | | | | | | | | | |
| All patients | 40 | 21 | 796 (645) | 696 | 631 (538) | 498 | 0.476 | 18.5 (8.4) | 14.2 (6.7) | 0.046 |
| Completers | 20 | 17 | 927 (673) | 736 | 725 (554) | 705 | 0.478 | 18.8 (7.9) | 15.3 (7.0) | 0.171 |

**Table 4** Cumulative dose MTX until the first recorded adverse event and dose MTX in the month prior to the first recorded event for each of the seven main predefined categories of adverse events.

Values are mean (SD) and median. TC= intensive treatment strategy group; CT= conventional treatment strategy group; n= number of patients with available data; GI symptoms= gastrointestinal symptoms; CNS= central nervous system.

Seventy patients in the TC strategy and 40 patients in the CT strategy had ALT abnormalities, after starting treatment with MTX, of whom 14 and 3 patients, respectively, had at least one recorded value >3xULN. Of the patients with AST abnormalities (63 in the TC strategy and 30 in the CT strategy), one patient in the CT strategy had at least one recorded value >3xULN. In the patients with liver enzyme elevations (>3xULN), the dose of MTX was reduced or stopped and started again after resolution for 13 patients, MTX was discontinued and not started for one patient and for three patients it led to withdrawal from the study.

For completers in the TC strategy, the average (SD) cumulative dose of MTX over two years was 2007 (691) mg for patients with liver toxicity and 1878 (783) mg for patients without liver toxicity (p=0.396). Similar observations were found in the CT strategy (respectively, 1662 (418) mg vs. 1602 (599) mg, p=0.556).

In both strategy groups, no clinical or demographic factors were found to be associated either with an abnormal value of AST or with ALT (see Table 5). An abnormal value of ALT was solely predicted by a high ALT level before the start of MTX in the TC strategy and an increased ALT and creatinine levels in the CT strategy. No associations between baseline values and abnormal value of AST were found in the TC strategy, but in the CT strategy an increase in both AST and ALT at study entry was associated with an abnormal value of AST during follow-up. Also, in the group of patients with liver enzyme levels <ULN at baseline, higher baseline enzymes were associated with abnormalities during the study.

## DISCUSSION

In this study the occurrence of AEs in patients with early RA who were treated according to an intensive treatment strategy or a conventional treatment strategy with MTX was described. Although more patients in the TC strategy experienced possible MTX related AEs than patients in the CT strategy, the severity of AEs was relatively mild and often reversible in both groups.

For 5% of the study population ALT levels >3xULN were recorded, but they did not result in serious clinical signs or symptoms of hepatitis or cirrhosis. No patients experienced pneumonia, in agreement with results of a large population study.[19] Four patients (1.4%) had reversible pancytopenia in our study, similar to the percentage found in a review.[20] Since patients were allowed to take NSAIDs, and cyclosporine could be used in the strategy regime, the reported AEs might not exclusively have been related to MTX therapy.

The average dose of MTX in the month before the first recorded event was higher in the TC strategy than in the CT strategy, but the median cumulative dose MTX until the first event was not. An explanation might be the faster incremental rise of the MTX dose in the TC strategy. However, the clinical efficacy of the intensive strategy was far better than of the conventional strategy, [15] which in our opinion outweighs the observed AEs.

| Variables | TC strategy OR (95%CI) | p | CT strategy OR (95%CI) | p |
|---|---|---|---|---|
| ALT | | | | |
| Age (years) | 1.015 (0.99-1.04) | 0.200 | 1.005 (0.98-1.03) | 0.672 |
| Gender (female vs. male) | 1.163 (0.58-2.35) | 0.673 | 0.597 (0.28-1.29) | 0.190 |
| BMI (kg/m$^2$) | 1.084 (0.97-1.21) | 0.141 | 1.116 (1.00-1.25) | 0.051 |
| SJC (number) | 1.038 (0.99-1.10) | 0.165 | 1.025 (0.96-1.09) | 0.445 |
| TJC (number) | 1.019 (0.97-1.07) | 0.407 | 1.002 (0.95-1.06) | 0.939 |
| VAS pain (mm) | 0.996 (0.98-1.01) | 0.586 | 0.998 (0.98-1.01) | 0.771 |
| VAS general well-being (mm) | 1.003 (0.99-1.02) | 0.712 | 1.009 (0.99-1.03) | 0.346 |
| Functional disability (HAQ) | 0.882 (0.51-1.15) | 0.653 | 1.208 (0.67-2.20) | 0.535 |
| ESR (mm/hr$^{1st}$) | 1.009 (1.00-1.02) | 0.166 | 1.000 (0.99-1.02) | 0.957 |
| Creatinine (µmol/l) | 0.994 (0.97-1.02) | 0.631 | 1.033 (1.00-1.07) | 0.038 |
| Creatinine clearance (ml/min) | 0.997 (0.98-1.01) | 0.591 | 1.005 (0.99-1.02) | 0.471 |
| AST (U/L) | 1.012 (0.97-1.06) | 0.576 | 1.039 (0.99-1.09) | 0.110 |
| ALT (U/L) | 1.031 (1.00-1.06) | 0.036 | 1.076 (1.04-1.12) | <0.01 |
| RF (positive vs. negative) | 1.196 (0.58-2.49) | 0.632 | 1.038 (0.46-2.34) | 0.929 |
| AST | | | | |
| Age (years) | 1.017 (0.99-1.04) | 0.163 | 1.022 (0.99-1.05) | 0.124 |
| Gender (female vs. male) | 1.125 (0.58-2.28) | 0.742 | 1.093 (0.47-2.57) | 0.838 |
| BMI (kg/m$^2$) | 1.053 (0.95-1.17) | 0.317 | 1.005 (0.89-1.13) | 0.930 |
| SJC (number) | 0.990 (0.94-1.04) | 0.705 | 0.981 (0.92-1.05) | 0.596 |
| TJC (number) | 0.984 (0.94-1.03) | 0.505 | 0.980 (0.92-1.05) | 0.545 |
| VAS pain (mm) | 0.999 (0.99-1.01) | 0.935 | 0.990 (0.97-1.01) | 0.241 |
| VAS general well-being (mm) | 1.004 (0.99-1.02) | 0.642 | 1.001 (0.98-1.02) | 0.943 |
| Functional disability (HAQ) | 0.879 (0.51-1.53) | 0.647 | 1.004 (0.53-1.92) | 0.990 |
| ESR (mm/hr$^{1st}$) | 1.011 (1.00-1.02) | 0.091 | 1.003 (0.99-1.02) | 0.732 |
| Creatinine (µmol/l) | 1.008 (0.98-1.03) | 0.541 | 1.021 (0.99-1.05) | 0.204 |
| Creatinine clearance (ml/min) | 0.993 (0.98-1.01) | 0.297 | 0.985 (0.97-1.00) | 0.072 |
| AST (U/L) | 1.038 (0.99-1.08) | 0.090 | 1.068 (1.02-1.12) | 0.009 |
| ALT (U/L) | 1.002 (0.98-1.03) | 0.874 | 1.065 (1.03-1.10) | 0.001 |
| RF (positive vs. negative) | 1.906 (0.90-4.05) | 0.093 | 0.527 (0.22-1.26) | 0.148 |

**Table 5** Possible association between baseline data and the risk of increased transaminase enzyme levels during follow-up.

Values show adjusted odds ratio's (adjusted for NSAID use at baseline). TC strategy= intensive treatment strategy group; CT strategy= conventional treatment strategy group; OR+ odds ratio; 95%CI= 95% confidence interval; ALT= serum aspartate aminotransferase; BMI= body mass index; SJC= swollen joint count; TJC= tender joint count; VAS= visual analogue scale (range 0-100 mm, worst score); HAQ= Health Assessment Questionnaire (0-3, most functional disability); ESR= erythrocyte sedimentation rate; AST= serum alanine aminotransferase; RF= rheumatoid factor.

The cumulative dose of MTX did not differ between completers with and without liver toxicity, but for 48% of the patients in the TC strategy and 33% of the patients in the CT strategy the dose of MTX was at least on one occasion not increased during one of the protocol visits because of abnormal laboratory values, although an increase was indicated according to protocol. We did not take oral MTX or scMTX administration into account in calculating the cumulative dose of MTX until each event. Since more patients in the TC strategy received

scMTX, the absorbed dose of MTX in the TC strategy may have been higher, although a discrepancy in bioavailability is mainly seen at higher doses of MTX.[21,22]
In this study, only a higher BMI was significantly associated with withdrawal due to MTX related AEs in the multiple regression analyses. However, only 58% of patients could be included in these analyses owing to missing baseline data. Interestingly, increased self reported pain, but none of the variables of the response criteria for dose adjustments (ESR, TJC, and VAS general well-being), was independently associated with withdrawal due to MTX and/or cyclosporine related AEs. These results are partly in agreement with those of other studies,[9-14] but we did not find any association with gender, age, and HAQ and MTX related withdrawal.
Because impaired renal function may lead to accumulation of MTX, we evaluated the association between renal function with withdrawal due to MTX related AEs and liver toxicity. In some previous studies no association between creatinine levels and MTX toxicity was found,[23,24] whereas in one study, pooling data from 11 individual studies, patients with diminished creatinine clearance were more likely to have a higher overall toxicity score.[13] In our study, there was a trend towards an association between impaired creatinine clearance and withdrawal due to MTX related AEs. Diminished creatinine clearance was not associated with liver toxicity, but we found that increased ALT, AST, and creatinine levels measured at the start of the start were significantly associated with liver toxicity at follow-up in both strategy groups.
In conclusion, the frequency of AEs in the TC strategy was higher than that in the CT strategy, but the severity of AEs was relatively mild. Since the clinical benefit in the TC strategy evidently was more pronounced, the efficacy / toxicity ratio supports intensive treatment with MTX as first (in case of step-up therapy) or anchor DMARD (in case of combination therapy) in early RA in daily practice. When starting MTX in patients with early RA, attention should be given to a high BMI, increased levels of serum liver enzymes, and decreased renal function.

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## REFERENCES


1. Jobanputra P, Wilson J, Douglas K, et al. A survey of British rheumatologists' DMARD preferences for rheumatoid arthritis. Rheumatology (Oxford) 2004; 43:206-10.
2. Sany J, Anaya JM, Lussiez V, et al. Treatment of rheumatoid arthritis with methotrexate: a prospective open longterm study of 191 cases. J Rheumatol 1991; 18:1323-7.
3. van Jaarsveld CH, Jahangier ZN, Jacobs JW, et al. Toxicity of anti-rheumatic drugs in a randomized clinical trial of early rheumatoid arthritis. Rheumatology (Oxford) 2000; 39:1374-82.
4. Morand EF, McCloud PI, Littlejohn GO. Life table analysis of 879 treatment episodes with slow acting antirheumatic drugs in community rheumatology practice. J Rheumatol 1992; 19:704-8.
5. Alarcon GS, Tracy IC, Strand GM, et al. Survival and drug discontinuation analyses in a large cohort of methotrexate treated rheumatoid arthritis patients. Ann Rheum Dis 1995; 54:708-12.
6. Kremer JM, Phelps CT. Long-term prospective study of the use of methotrexate in the treatment of rheumatoid arthritis. Update after a mean of 90 months. Arthritis Rheum 1992; 35:138-45.
7. Suarez-Almazor ME, Belseck E, Shea B, et al. Methotrexate for rheumatoid arthritis. Cochrane Database Syst Rev 2000; CD000957.
8. Alarcón GS, Tracy IC, Blackburn WD Jr. Methotrexate in rheumatoid arthritis. Toxic effects as the major factor in limiting long-term treatment. Arthritis Rheum 1989; 32:671-6.
9. Walker AM, Funch D, Dreyer NA, et al. Determinants of serious liver disease among patients receiving low-dose methotrexate for rheumatoid arthritis. Arthritis Rheum 1993; 36:329-35.
10. Hoekstra M, van Ede AE, Haagsma CJ, et al. Factors associated with toxicity, final dose, and efficacy of methotrexate in patients with rheumatoid arthritis. Ann Rheum Dis 2003; 62:423-6.
11. Suzuki Y, Uehara R, Tajima C, et al. Elevation of serum hepatic aminotransferases during treatment of rheumatoid arthritis with low-dose methotrexate. Risk factors and response to folic acid. Scand J Rheumatol 1999; 28:273-81.
12. Kent PD, Luthra HS, Michet C Jr. Risk factors for methotrexate-induced abnormal laboratory monitoring results in patients with rheumatoid arthritis. J Rheumatol 2004; 31:1727-31.
13. Rheumatoid Arthritis Clinical Trial Archive Group. The effect of age and renal function on the efficacy and toxicity of methotrexate in rheumatoid arthritis. J Rheumatol 1995; 22:218-23. 14.
14. Hider SL, Silman AJ, Thomson W, et al. Can clinical factors at presentation be used to predict outcome of treatment with methotrexate in patients with early inflammatory polyarthritis? Ann Rheum Dis 2009; 68:57-62.
15. Verstappen SM, Jacobs JW, van der Veen MJ, et al. Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open-label strategy trial). Ann Rheum Dis 2007; 66:1443-9.
16. 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.
17. Kremer JM, Alarcon GS, Lightfoot RW Jr, et al. Methotrexate for rheumatoid arthritis. Suggested guidelines for monitoring liver toxicity. American College of Rheumatology. Arthritis Rheum 1994; 37:316-28.
18. Whitworth JA; World Health Organization, International Society of Hypertension Writing Group. 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. J Hypertens 2003; 21:1983-92.
19. Wolfe F, Caplan L, Michaud K. Treatment for rheumatoid arthritis and the risk of hospitalization for pneumonia: associations with prednisone, disease-modifying antirheumatic drugs, and anti-tumor necrosis factor therapy. Arthritis Rheum 2006; 54:628-34.
20. Gutierrez-Ureña S, Molina JF, García CO, et al. Pancytopenia secondary to methotrexate therapy in rheumatoid arthritis. Arthritis Rheum 1996; 39:272-6.
21. Hoekstra M, Haagsma C, Neef C, et al. Bioavailability of higher dose methotrexate comparing oral and subcutaneous administration in patients with rheumatoid arthritis. J Rheumatol 2004; 31:645-8.
22. Hamilton RA, Kremer JM. Why intramuscular methotrexate may be more efficacious than oral dosing in patients with rheumatoid arthritis. Br J Rheumatol 1997; 36:86-90.

23. McKendry RJ, Dale P. Adverse effects of low dose methotrexate therapy in rheumatoid arthritis. J Rheumatol 1993; 20:1850-6.
24. 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.

Chapter 4

# Are switches from oral to subcutaneous MTX or addition of cyclosporine to MTX useful steps in a tight control treatment strategy for RA? A post-hoc analysis of the CAMERA study

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## ABSTRACT

### Objective

To investigate the usefulness of a switch from oral methotrexate (MTX) to (same dose) subcutaneous MTX (scMTX) or adding cyclosporine to oral MTX with a simultaneous reduction of the MTX dose (max 15 mg/wk), in case of adverse events or insufficient effect of maximum (tolerable) dose oral MTX treatment.

### Methods

The tight control treatment arm of the CAMERA trial was evaluated. The change in disease activity (DAS28) after taking scMTX (over 1 month) or adding cyclosporine (over 3 months) was compared to the average 3 monthly change before the strategy step. Analyses were performed for each strategy step and separately for the strategy steps because of adverse events or insufficient effect. Additionally, analyses of individual responses were performed.

### Results

Of the 151 patients, 57 needed the scMTX strategy step (21 because of adverse events, 36 because of insufficient effect) and 40 the following cyclosporine strategy step (20 and 20, respectively). The decrease in DAS28 after taking the scMTX strategy step was 0.30 points ($p<0.05$); 0.21 points more decline (ns) compared to the average 3 monthly change before the step; no significant change in DAS28 was seen after the cyclosporine strategy step. For the strategy steps because of adverse events or insufficient effect separately, 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 cyclosporine step seems ineffective.

## INTRODUCTION

Treatment of patients with early rheumatoid arthritis (RA) as early as possible after the diagnosis has been made is important to prevent joint destruction and functional disability in the long-term.[1] Nowadays patients with early RA commonly start treatment with methotrexate (MTX), the most frequently used disease modifying anti-rheumatic drug (DMARD) for RA.[2] Besides treating as early as possible, tight control is another important principle in RA treatment that leads to better outcomes in the long-term.[3-6] Tight control can be defined as a treatment strategy tailored to the disease activity of the individual RA patient with the aim of achieving a predefined level of low disease activity, preferably remission, within a reasonable period of time.[3] One of the studies which demonstrated the benefit of this principle is the Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA) trial, showing that after two years of treatment, an intensive (tight control) strategy resulted in better clinical effects compared to a conventional strategy.[7] After two years of treatment, 50% of the patients in the intensive strategy were in remission versus 37% of the patients in the conventional strategy (p=0.03).

Patients in the CAMERA trial were treated with oral MTX in stepwise increasing dosages according to the treatment strategy. In case of insufficient efficacy after the maximum dose of MTX (30 mg/wk) or in case of adverse events, the next treatment strategy step was a switch to (same dose) subcutaneous MTX administration (scMTX) and subsequently the addition of cyclosporine with a reduction of oral MTX (to maximum of 15 mg/wk). Although the results of the CAMERA trial indicate that intensive (tight control) treatment is more effective than conventional treatment, the efficacy of the treatment strategy steps described above within the total strategy is not clear. In fact this is hardly ever studied in treatment strategy studies. The aim of the present evaluation is therefore to analyze the effectiveness of the scMTX strategy step and cyclosporine strategy step as used within the tight control treatment strategy of the CAMERA trial as next steps after reaching the maximum (tolerable) oral MTX dose, in case remission was not yet present.

## PATIENTS AND METHODS

Patients who participated in the tight control arm of the two-year randomised, open-label prospective multi-centre treatment strategy (CAMERA) trial were evaluated.[7] 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, were DMARD-naïve, and were not using glucocorticoids. In the tight control arm, the intensive MTX treatment strategy was guided by (computer assisted) monthly predefined response criteria. The medical ethics committees of all participating hospitals approved this trial, and all patients gave written informed consent before entering the trial.

**Treatment strategy**

All patients started with 7.5 mg/wk oral MTX with daily folic acid (0.5 mg/day, except for the day of MTX intake). At each monthly visit, data on swollen joint count (SJC), tender joint count (TJC), erythrocyte sedimentation rate (ESR), and visual analogue scale (VAS) for general well-being were collected and entered in a computer decision program by the rheumatologist. The program calculated whether or not predefined criteria of response (>20% improvement in SJC and in two out of TJC, ESR, and VAS compared to previous visit) were met. In case of insufficient response, the dosage was increased stepwise by 5 mg/wk until remission was reached or until the maximum dose oral MTX of 30 mg/wk or the maximum tolerable dose was reached. The dosage MTX was not changed if patients fulfilled the response criteria compared to their previous visit or if remission (defined as SJC=0, and two out of the following criteria: TJC ≤5, ESR ≤20 mm/hr, and VAS ≤20 mm) was reached.[7] If patients fulfilled the predefined goal of sustained remission, defined as remission during 4 subsequent visits,[7] MTX was stepwise reduced by 2.5 mg/wk each month as long as patients fulfilled the remission criteria; otherwise the dose of MTX was increased as described above.

In case the maximum dose oral MTX was reached and patients did not meet the predefined goal of remission, the same dose of MTX was administered subcutaneously (scMTX; dose 30 mg/wk). For patients on scMTX who thereafter still did not meet the predefined goal of remission at the subsequent visit, cyclosporine (starting dose 2.5 mg/kg/d; increased stepwise by 0.5 mg/kg/d monthly until maximum dose of 4.0 mg/kg/d) was added to the MTX therapy. In that case, the MTX dose was decreased to 15 mg/wk orally because of the negative effect of cyclosporine on kidney function, possibly increasing MTX toxicity.

In case of maximum tolerable dose of oral MTX because of adverse events to oral MTX (mainly gastrointestinal), the patient was treated with scMTX (the same dose and escalation scheme as used orally) followed by adding cyclosporine (in combination with a maximum of 15 mg/wk oral MTX) in case of insufficient effect at maximum dose scMTX (30 mg/wk). In case of serious adverse events (i.e. leukocyte count $\leq 2.5 \times 10^9$/l, thrombocyte count $\leq 100 \times 10^9$/l or pneumonitis) with oral MTX use, the scMTX step was skipped.

**Effectiveness of treatment strategy steps**

The effectiveness of the scMTX strategy step was evaluated at one month after starting scMTX. The effect of the cyclosporine strategy step, with increasing dosages and a more delayed response (and the extra step of restricting MTX dose to a maximum of 15 mg/wk), was evaluated at 3 months after the strategy step. The effectiveness of the strategy step was calculated by comparing the change in disease activity score (DAS28) at 1 or 3 months, respectively, with the average monthly change over the 3 monthly intervals directly preceding the treatment step.

Analyses were performed for both strategy steps and separately for patients who took the steps because of adverse events or because of insufficient effect of treatment.

**Statistical analyses**

To evaluate if there was a trend in the course of the DAS28 repeated measures analysis were calculated over the 4 months evaluation period for the scMTX strategy step and the 6 months evaluation period for the cyclosporine strategy step (i.e. including the three months before the strategy steps).

The average monthly change in DAS28 in the preceding 3 months and the change in DAS28 after taking the scMTX strategy step (1 month) or cyclosporine strategy step (3 months) were tested for statistical significance using the paired sample T-tests.

Individual responses were calculated by subtracting the individual mean monthly DAS28 change in the 3 months preceding the treatment strategy step from the DAS28 change at 1 month (scMTX strategy step) or the DAS28 change at 3 months (cyclosporine strategy step). The strategy step was considered effective for the patient when this difference was less than zero, indicating at least an equal decline in the disease activity score after taking the step compared to before taking the step. Note that the actual response percentage as calculated in this way is also dependent on the change in DAS28 before the strategy step.

The statistical software SPSS 15.0 was used for analyses of data. A p value $<0.05$ was considered to be statistically significant.

**RESULTS**

151 patients had been treated according to the intensive (tight controlled) treatment strategy. In total, 57 patients needed the scMTX strategy step, 21 because of adverse events, and 36 because of insufficient effect. Forty patients needed the cyclosporine strategy step, 20 because of adverse events and 20 because of insufficient effect. Seven patients of those who took the cyclosporine strategy step because of adverse events did not take the scMTX strategy step first and two patients stopped all MTX treatment because of serious adverse events due to MTX.

The characteristics of the patients who needed the scMTX and cyclosporine strategy step at the moment of taking these strategy steps are shown in Table 1. Patients who took the scMTX strategy step because of adverse events did this on average after 14 visits (50 (27) weeks; mean (SD)) and had a mean dose of 25 (6.5) mg/wk of (oral) MTX before taking this step, whereas patients who took the step because of insufficient effect did this on average after 11 visits (38 (14) weeks) of treatment and had a maximum dose of 30 mg/wk according to the strategy.

The cyclosporine strategy step because of adverse events was taken on average after 16 visits (58 (27) weeks); at that moment the patients had a mean dose of 26 (7.9) mg/wk of (oral or sc) MTX. This was 14 visits (50 (13) weeks) of treatment for patients who took the step because of insufficient effect and 30 mg/wk according to the strategy.

| | scMTX strategy step | | | cyclosporine strategy step | | |
|---|---|---|---|---|---|---|
| | total | AE | IE | total | AE | IE |
| Characteristic | n = 57 | n = 21 | n = 36 | n = 40 | n = 20 | 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/h$^{1st}$) | 23 (15) | 28 (19) | 20 (11) | 24 (19) | 27 (24) | 21 (12) |
| CRP (mg/l) | 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 |
| MTX dose (mg/wk) | 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) |

**Table 1** Characteristics of patients who took the scMTX strategy step or the (next) cyclosporine strategy step.

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. Total= total group of patients taking the strategy step; AE= patients taking the strategy step because of adverse events; IE= patients taking the strategy step because of insufficient effect; ESR= erythrocyte sedimentation rate [2-140 mm/h$^{1st}$]; CRP= C-reactive protein [0-150 mg/l]; RF$^{+}$= rheumatoid factor positive; morning stiffness= [0-180 min]; VAS= visual analogue scale [0 -100 mm (= worst score)]; TJC= tender joint count [0-26]; SJC= swollen joint count [0-26]; DAS28= disease activity score; SHS= SharpvanderHeijde score; MTX dose= dose (oral or sc) MTX when patients took the strategy step; time until step= number of visits compared to baseline (start study) after patients took the strategy step.

### Course of the disease activity score

The course of the DAS28 for the different groups is shown in Figure 1. Over the 4 month evaluation period there was a decreasing trend in the course of the DAS28 for patients who took the scMTX strategy step of 0.5 points, this difference between baseline (i.e. start with strategy step) and 4 months was statistically significant ($p<0.01$) (solid line Figure 1A). This trend was observed for the change because of adverse effects (dashed line, 0.4 points; ns) and because of insufficient effect (dotted line, 0.6 points; $p<0.001$). For the cyclosporine strategy step, there was no trend over time in the DAS28 over the 6 months evaluation period ($p=0.37$; solid line Figure 1B). This observation was similar for the treatment strategy shift because of adverse effects (dashed line; ns) and because of insufficient effect (dotted line; ns).

The mean change in the DAS28 one month after taking the scMTX strategy step was 0.30 points ($p<0.05$); 0.21 points more decline (ns) than the mean improvement in the DAS28 before taking the step. Again quite similar results were seen for the change in treatment because of adverse effects and because of insufficient effect (see Figure 1A). Note that no

difference means that the mean monthly decrease in DAS28 over the past 3 months is continued. Thus scMTX resulted in a further decrease in DAS28.

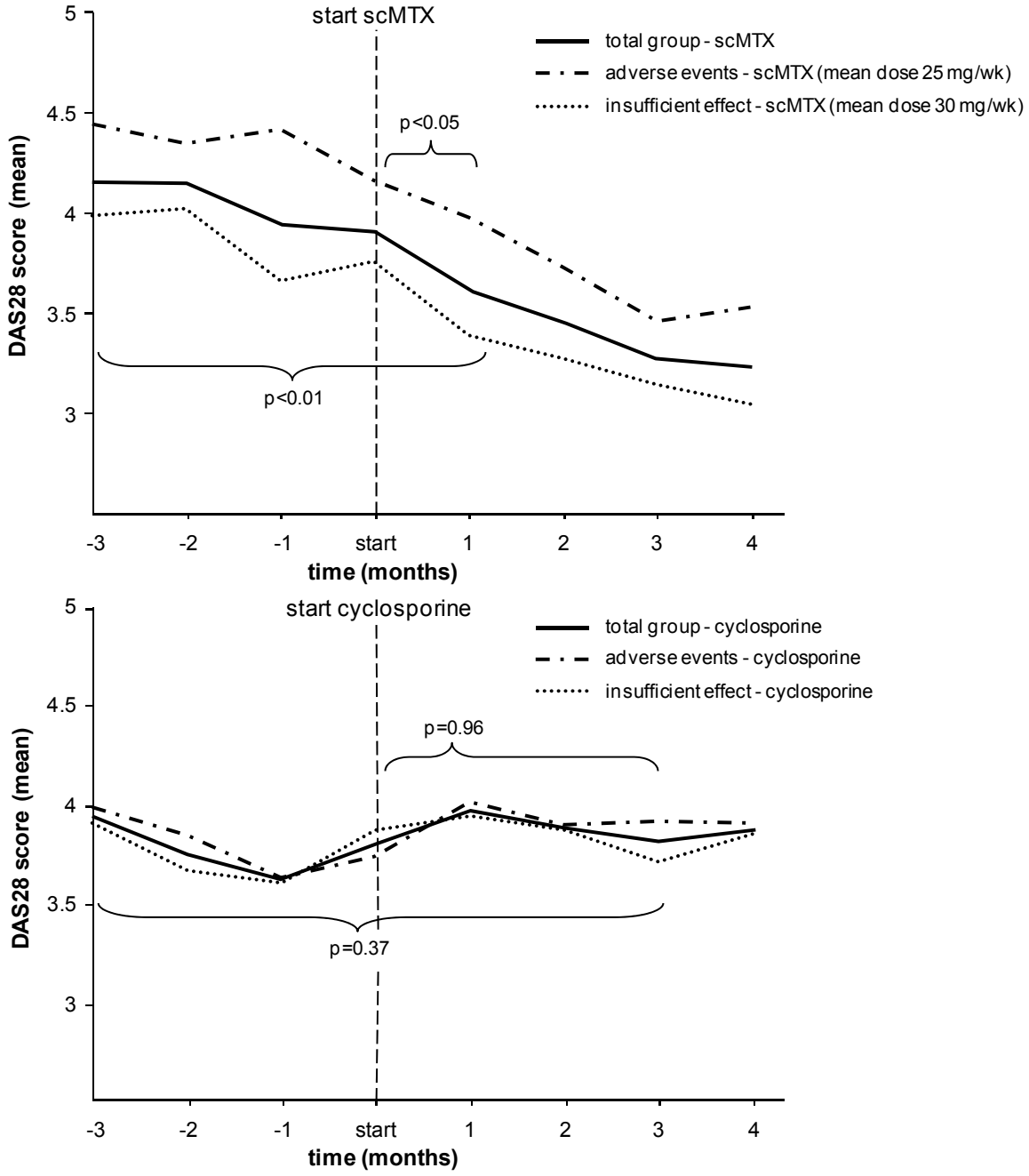


**Figure 1A-B.** The course of the DAS28 for patients who took the subcutaneous methotrexate (scMTX) strategy step (A) or the cyclosporine strategy step (B). The solid lines show the course of the DAS28 for the total groups of patients taking scMTX or cyclosporine strategy steps, the dashed lines show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

In contrast, the change in the DAS28 three months after taking the cyclosporine strategy step was 0.01 points increase in DAS28 (ns); which was 0.06 points worse compared to the mean improvement in the DAS28 before taking the step (ns). The results were similar for the strategy steps because of adverse effects and because of insufficient effect separately (see Figure 1B).

**Individual responses to the scMTX or cyclosporine strategy step**

The switch to scMTX led to a further improvement of the DAS28 in 36 patients (63%, 95%CI 50 to 70%) whereas in 21 it did not further improve (Figure 2A); 6 of these 21 improved a little but not more than the decline in DAS28 present before the switch (i.e. the improvement before switch was too small to meet the predefined criteria of response). In contrast, in the cyclosporine group less than half of the 19 patients (48%, 95%CI 32 to 64%) showed improvement compared to the previous three months evaluation, whereas 21 did not further improve (Figure 2B). In fact in 20 of these 21 patients the DAS28 deteriorated after the cyclosporine strategy step. Note that the course of the disease activity before taking the switch to scMTX showed a significant decrease, but that for the patients taking the cyclosporine group, the DAS28 showed virtually no change.

With respect to the subgroups for each of the strategy steps; in the scMTX strategy step the response rates are 57% and 67% for patients who took the step because of adverse events or insufficient effect, and for patients in the cyclosporine strategy step 35% and 60%, respectively.

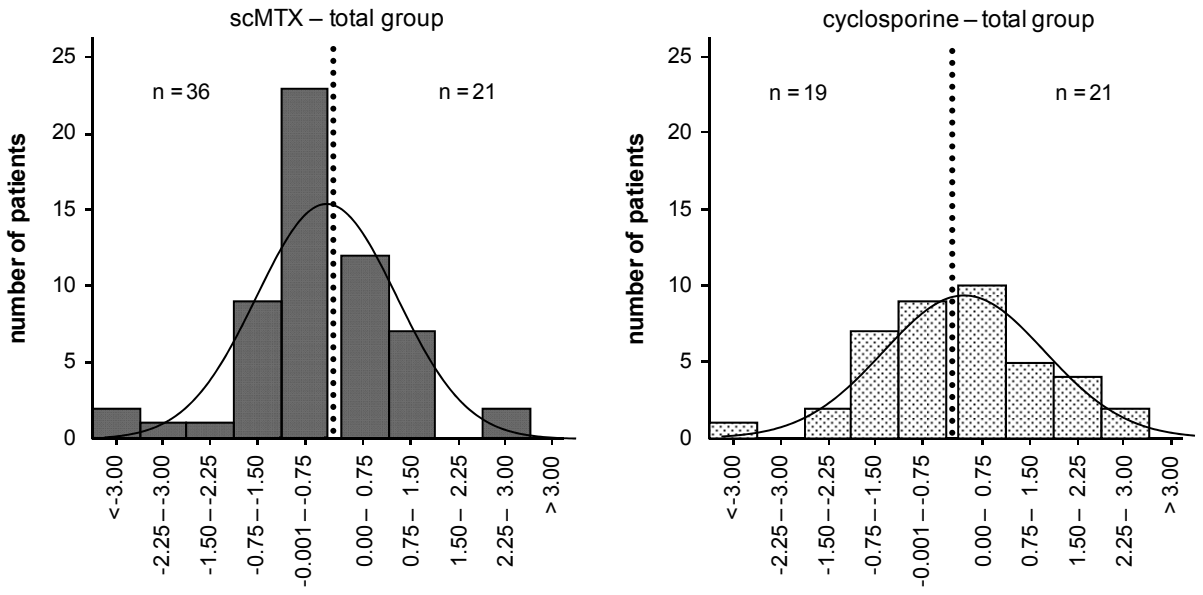


**Figure 2A-B.** The individual responses are presented as categorised changes, based on the differences between the individual mean monthly DAS28 change in the 3 months before taking the treatment strategy step minus the DAS28 change after 1 month (scMTX strategy step; A) or 3 months (cyclosporine strategy step; B) after taking the steps. Positive values mean 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.

## DISCUSSION

The results suggest that the scMTX strategy step after oral MTX was useful with regard to a further decrease in disease activity, specifically for the patients who have insufficient effect on 30 mg/wk MTX. In contrast, the cyclosporine strategy step seems to be less useful within the tight control strategy.

There are some limitations to this study. The analyses have been done within an existing strategy trial, which had not been designed to investigate the efficacy of the individual treatment strategy steps within the total treatment strategy. So no comparable control group was available to compare the results without a strategy step with those of the strategy steps. Our measure of effectiveness was therefore based on the change in the course of the disease activity of patients after taking the step compared with the average monthly change in the disease activity course before taking the step. This change was also used to compute individual response. In this comparison no difference was used as a cut off point for response considering the patient population and place in the treatment strategy.

A reason scMTX is a successful strategy step could be the higher bioavailability compared to oral MTX.[8] The average DAS28 over the 3 months before the start of the strategy step was used to (as much as possible) correct for potential natural fluctuations in disease activity and for bias such as regression to the mean. For both patients who took the step due to insufficient effect and (to a lesser degree) those who took it because of adverse events, the switch of oral to scMTX seems useful.

In accordance with our data, another randomised controlled trial (RCT) with MTX-naïve, early RA patients showed that starting with scMTX was more efficient than starting with oral MTX treatment at the same dosage of 15 mg/week. Respectively 78% and 70% of patients achieved an ACR20 response after 24 weeks of treatment.[9] Another study showed that patients with juvenile idiopathic arthritis failing oral MTX either because of inefficacy or toxicity had a high likelihood of success by switching from oral to scMTX. After the switch more than 70% of the patients achieved the defined criteria for improvement ($p<0.05$), without increased toxicity.[10]

An explanation for the less effective cyclosporine strategy step might be that most of the patients who needed the cyclosporine step already had failed on the (subcutaneous and oral) MTX treatment before; these could be a subset of patients resistant to medication. Also the decrease in the dose MTX has to be taken into account. Most patients who used scMTX were on 30 mg/wk at the moment of taking the cyclosporine strategy step. The next strategy step of cyclosporine and only 15 mg/wk oral MTX could be a reason why patients who took the cyclosporine strategy step did not show an improvement. Regarding cyclosporine, studies show that combination therapy of MTX and cyclosporine leads to a better clinical response when compared to monotherapy (MTX or cyclosporine alone).[11-13] However, in these RCTs combination therapy of cyclosporine and MTX was immediately started in (nearly) untreated RA patients as opposed to our study in which patients had to have insufficient response to MTX. Another study [14] investigated the effect of cyclosporine in

combination with MTX versus MTX and placebo in patients with (longstanding) severe RA who were previously treated with MTX alone with a maximum dose of 15 mg/wk and had partial response to treatment. Six months after start of treatment patients who were treated with combination therapy clinically had more improvement; 48% patients met the ACR20 criteria compared to 16% in the MTX and placebo group. However, these studies are not directly comparable to the cyclosporine strategy step in the CAMERA trial, because of the used tight control principle and differences in disease duration and starting point in treatment (partial response on 15 mg MTX versus no remission on 30 mg MTX).

There are several other studies investigating intensive treatment strategies in RA, for instance TICORA, BeSt, COBRA, and CIMESTRA.[4, 5, 12, 15] These strategies are effective although they differ and efficacy of the individual steps within these strategies is not known. Therefore analyses like these, although suboptimal, are useful to determinate optimal tight control strategies from the different approaches used.

In conclusion, the scMTX strategy step seems a useful step after oral MTX in a tight control strategy in early RA, especially when taking the step because of insufficient effect, whereas the following cyclosporine step seems ineffective. Therefore, after failure of oral MTX it should be recommended to use scMTX as next step in the treatment strategy, whereas addition of cyclosporine can not be recommended.

**ACKNOWLEDGEMENTS**

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## REFERENCES


1. Boers M. Understanding the window of opportunity concept in early rheumatoid arthritis. *Arthritis Rheum* 2003;48:1771-4.
2. Visser K, van der Heijde D. Optimal dosage and route of administration of methotrexate in rheumatoid arthritis: a systematic review of the literature. *Ann Rheum Dis* 2009;68:1094-9.
3. Bakker MF, Jacobs JW, Verstappen SM, et al. Tight control in the treatment of rheumatoid arthritis: efficacy and feasibility. *Ann Rheum Di*s 2007;66 Suppl 3:iii56-60.
4. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. *Arthritis Rheum* 2005;52:3381-90.
5. Grigor C, Capell H, Stirling A, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. *Lancet* 2004;364:263-9.
6. Mottonen T, Hannonen P, Leirisalo-Repo M, et al. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. *Lancet* 1999;353:1568-73.
7. Verstappen SM, Jacobs JW, van der Veen MJ, et al. Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open label trial). *Ann Rheum Dis* 2007;66:1443-9.
8. Hoekstra M, Haagsma C, Neef C, et al. Bioavailability of higher dose methotrexate comparing oral and subcutaneous administration in patients with rheumatoid arthritis. *J Rheumatol* 2004;31:645-8.
9. 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.
10. Alsufyani K, Ortiz-Alvarez O, Cabral DA, et al. The role of subcutaneous administration of methotrexate in children with juvenile idiopathic arthritis who have failed oral methotrexate. *J Rheumatol* 2004;31:179-82.
11. Gerards AH, Landewé RB, Prins AP, et al. Cyclosporin A monotherapy versus cyclosporin A and methotrexate combination therapy in patients with early rheumatoid arthritis: a double blind randomised placebo controlled trial. *Ann Rheum Dis* 2003;62:291-6.
12. Hetland ML, Stengaard-Pedersen K, Junker P, et al. Aggressive combination therapy with intraarticular glucocorticoid injections and conventional DMARDs in early rheumatoid arthritis Two Year Clinical and Radiographic Results From The CIMESTRA Study. *Ann Rheum Dis* 2008;67:815-22.
13. Marchesoni A, Battafarano N, Arreghini M, et al. Radiographic progression in early rheumatoid arthritis: a 12-month randomized controlled study comparing the combination of cyclosporin and methotrexate with methotrexate alone. *Rheumatology (Oxford)* 2003;42:1545-9.
14. Tugwell P, Pincus T, Yocum D, et al. Combination therapy with cyclosporine and methotrexate in severe rheumatoid arthritis. The Methotrexate-Cyclosporine Combination Study Group. *N Engl J Med* 1995;333:137-41.
15. Boers M, Verhoeven AC, Markusse HM, et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. *Lancet* 1997;350:309-18.

Chapter 5

# Early clinical response to treatment predicts long-term outcome in RA patients: 5 year follow-up results of a MTX-based tight control strategy (CAMERA)

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*Ann Rheum Dis, conditionally accepted*

## ABSTRACT

### Objective

To investigate the long-term effects of the tight control MTX-based strategy compared to the conventional MTX-based strategy of the CAMERA trial in early RA and to investigate the predictive value of an early response to treatment for long-term outcome.

### Methods

The clinical and radiographic outcome at 5 years was compared between initial strategies. Patients were classified as early good-, moderate- or non-responders according to the EULAR response criteria. The prognostic value of early response to treatment in addition to established predictors was analysed by multiple linear regression analysis.

### Results

From 205 of 299 patients included, 5 years data was available (102 tight control, 103 conventional), with no indication for selective drop-out. At 5 years there was no significant difference for clinical and radiographic outcomes between the treatment strategies. For the tight control and conventional strategy, 47% and 23% were good-, 41% and 44% moderate-, and 12% and 33% non-responders, respectively. Early good-responders had a mean DAS28 of 2.39 (1.2) and median yearly progression rate of 0.6 (0.0-2.2) at 5 years; significantly lower (all $p<0.02$) when compared to early moderate- and non-response. Multiple regression analysis showed that early response to treatment is an independent predictor of long-term outcome, irrespective of treatment strategy.

### Conclusions

The difference in disease activity between treatment strategies disappeared over the years. An early good-response to treatment independently predicts significantly better long-term clinical and radiographic outcome irrespective of the treatment strategy. Probably, tight control needs to be continued in those patients who still have active disease.

## INTRODUCTION

To prevent a severe disease course and major joint damage which may lead to irreversible disability, it is important to treat early rheumatoid arthritis (RA) patients as soon as possible after diagnosis, within the generally appreciated 'window of opportunity', when the disease is believed to be the most responsive to treatment.[1] Nowadays the 'tight control' principle is considered an additional important concept in the treatment of RA patients. Tight control can be defined as a treatment strategy tailored to the disease activity of each individual RA patient with the aim of achieving a predefined level of low disease activity or preferably remission within a reasonable period of time.[2] For early RA, reasonably tight control should be perused within the window of opportunity. The tight control strategy has been found effective in the short-term; the long-term effectiveness is less clear.[2-5] Moreover, tight control studies show that with this approach 32 - 62% of the patients do not reach remission within two years of treatment. Possibly those patients need an even more intensive therapeutic strategy early in the disease; for them, if possible, decisions on efficacy of treatment preferentially should be made earlier in the disease course with potentially intensification of the (medication) strategy if needed.
Disease activity at baseline is predictive of remission at two years of treatment [6] and prediction models based on a combination of baseline variables are able to predict long-term outcome of RA, although not precise enough yet for individual patients in clinical practice.[7-11] Also early response to treatment may be of importance to predict the long-term outcome. Disease activity during the first three months of treatment was related to clinical and radiographic outcome after the first year of treatment but data on long-term outcome are lacking.[12-14]
The present study investigates the long-term effects of a 2-year MTX-based tight control treatment strategy compared to conventional MTX-based treatment strategy and the (added) predictive value of an early response to treatment for long-term (5 year) outcome of patients with respect to disease activity and progression of radiographic joint damage.

## PATIENTS AND METHODS

Patients who had participated in a two-year randomised, open-label prospective multi-centre treatment strategy trial, the Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA [15]), were evaluated. Patients had been included in this study between 1999 and 2003. At study entry all patients fulfilled the 1987 revised American College of Rheumatology (ACR) criteria for RA,[16] had a disease duration of less than 1 year, and were DMARD- and glucocorticoid-naïve. Patients were randomized to either the tight control MTX-based treatment strategy, based on computer guided monthly predefined response criteria, or to the conventional MTX-based strategy, 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), erythrocyte sedimentation rate (ESR), and visual analogue scale (VAS) for general well-being were collected at every visit by the rheumatologist. In the tight control strategy these data were entered in a computer decision program by the rheumatologist at each monthly visit. The program calculated whether or not predefined criteria for response (>20% improvement in SJC and in two out of TJC, ESR, and VAS compared to previous visit) were met. If not, the strategy was intensified. For the conventional treatment strategy, dose adjustments were based on the opinion of the treating rheumatologist at each 3-monthly visit (mainly focused on the SJC). In both strategies also joint damage was assessed on radiographs of hands and feet at baseline and subsequent yearly.
In the first 2 years for both strategies DMARD medication was restricted to oral MTX, starting with 7.5 mg/wk up towards a maximum oral MTX dose of 30 mg/wk. This was followed by subcutaneous MTX (scMTX) in case of insufficient response on 30 mg/wk oral MTX or already earlier in case of subjective/mild adverse events to oral MTX, and as next step cyclosporine with reduction in oral MTX to 15 mg/wk (or maximum tolerable dose) in case of insufficient response to scMTX. Cyclosporine could be started directly after oral MTX in case of severe adverse events to oral MTX. After the 2-year trial, medication was free. The medical ethics committees of all participating hospitals approved this study, and all patients gave written informed consent before entering the study.

**EULAR response criteria**

At 6 months, patients were classified as early good responders, early moderate responders or early non responders according to the EULAR response criteria.[17] These criteria are based on the disease activity score (DAS28) at a certain time point and the improvement of the DAS28 from baseline (start of treatment) until that time point. The DAS28 [18] is based on the TJC and SJC of 28 joints, ESR, and a VAS general well-being. Good responders have a DAS28 score ≤3.2 and an improvement >1.2; non responders a DAS28 score >5.1 and an improvement between 0.6 and 1.2 or only an improvement ≤0.6. Patients with a response in between the good and non responders are classified as moderate responders. The response groups are referred to as ‘early good-responders’, ‘early moderate-responders’ and ‘early non-responders’.

**Long-term outcome**

Disease activity and radiographic joint damage were investigated at 5 years of treatment.
Disease activity was assessed by DAS28 or if it was not available, by the mean DAS28 of 4 and 6 years, or the DAS28 at 4 or at 6 years of treatment, depending on the data available.
For joint damage, radiographs of hand and feet were evaluated according to the SharpvanderHeijde score (SHS) [19] by 2 readers, blinded to clinical information. The mean yearly radiographic progression rate between baseline and 5 years was used as outcome measure. For this rate, if 5 year radiographs were not available, the mean of the

measurements between 4 and 6 years were used, or scores at 4 or 6 years, depending on the data available.

**Statistical analyses**

DAS28 at 5 years and mean yearly radiographic progression rate over 5 years were compared between the treatment strategies and tested for significant differences with independent t-tests. For analyses log transformed scores (log (progression rate +1)) was used since scores were not normally distributed.

DAS28 at 5 years and mean yearly radiographic progression rate over 5 years were compared between the early good-, moderate-, and non-response and tested with ANOVA and independent t-tests.

To investigate whether an early response to treatment has additional predictive value over well known predictors (rheumatoid factor (RF) and baseline disease activity or joint damage) multiple linear regression analysis was used (with treatment strategy, age, and gender as covariates next to predictors). In this analysis non-response was the reference category for early response (two dummy variables).

Since the early (6 month) response might have a different meaning in the two treatment strategies, due to the different timing and use of treatment, this was also investigated in the regression analysis. The interaction between treatment strategy and response to treatment was investigated by creating 6 categories (i.e. tight control (TC) good-, TC moderate- and TC non-responders, and conventional treatment (CT) good-, CT moderate-, and CT non-responders), using non-response in the conventional treatment strategy as reference category.

Finally, the influence of missing data on results was investigated using multivariate imputation.

SPSS 15.0 was used for the analyses. A p-value <0.05 was considered statistically significant.

**RESULTS**

Baseline characteristics and demographics for all patients and for patients with available long-term data in both treatment strategies are given in Table 1A.

Of 205 of 299 patients included 5 years data was available (102 tight control and 103 conventional strategy); 68 patients (34%) were early good-, 84 (43%) early moderate-, and 45 patients (23%) early non-responders. For 8 patients no early EULAR response could be calculated due to missing scores. For the tight control strategy 47%, 41%, and 12% were early good-, moderate-, and non-responders and for the conventionally treated group this was 23%, 44%, and 33%, respectively (Table 1B). Data show that patients' and disease characteristics were similar between all patients and patients with available long-term data and also between treatment strategies.

| | $CAMERA_{total}$ | $DAS28_{complete}$ | | $Radiograph_{complete}$ | |
|---|---|---|---|---|---|
| Characteristic | **all** n = 299 | **TC** n = 102 | **CT** n = 103 | **TC** n = 97 | **CT** n = 103 |
| Female gender (%) | 201 (67) | 72 (71) | 66 (64) | 67 (69) | 65 (63) |
| Age (years) | 53 (15) | 54 (13) | 53 (14) | 53 (13) | 52 (14) |
| ESR (mm/$h^{1st}$) | 37 (26) | 37 (28) | 38 (21) | 36 (28) | 38 (23) |
| CRP (mg/l) | 28 (28) | 28 (31) | 30 (25) | 28 (33) | 30 (27) |
| RF positive (%) | 185 (62) | 90 (65) | 67 (65) | 65 (67) | 64 (62) |
| Morning stiffness (min) | 92 (61) | 66 (65) | 88 (59) | 95 (66) | 89 (59) |
| VAS-GH (mm) | 54 (24) | 54 (24) | 54 (23) | 55 (24) | 53 (24) |
| VAS pain (mm) | 51 (27) | 53 (28) | 49 (28) | 53 (28) | 49 (27) |
| TJC | 14 (7) | 15 (7) | 13 (7) | 15 (8) | 14 (7) |
| SJC | 14 (7) | 14 (7) | 14 (6) | 14 (7) | 14 (7) |
| DAS28 | 5.6 (1.1) | 5.6 (1.2) | 5.6 (1.0) | 5.6 (1.1) | 5.6 (1.0) |
| SHS | 0 (0-0) | 0 (0-0) | 0 (0-0) | 0 (0-0) | 0 (0-0) |

**Table 1A** Baseline demographic and clinical characteristics of all patients in the CAMERA trial and patients with complete long-term data on long-term outcome.

Mean (SD) is shown for all continuous variables, except for SHS where median (IQR) is shown. For all categorical variables number (%) of patients is shown. $CAMERA_{total}$= all available data on all patients included (ITT population); TC= tight control treatment strategy; CT= conventional treatment strategy; ESR= erythrocyte sedimentation rate; CRP= C-reactive protein; RF= rheumatoid factor, VAS= visual analogue scale; VAS-GH= visual analogue scale general well-being; TJC= tender joint count, based on 38 joints; SJC= swollen joint count, based on 38 joints; DAS28= disease activity score based on 28 joint count; SHS= SharpvanderHeijde score.

| | $CAMERA_{tota}$ | | $DAS28_{complete}$ | | $Radiograph_{complete}$ | |
|---|---|---|---|---|---|---|
| Characteristic | **TC** n = 151 | **CT** n = 148 | **TC** n = 102 | **CT** n = 103 | **TC** n = 97 | **CT** n = 103 |
| Early good-response (%) | 67 (48) | 34 (25) | 45 (47) | 23 (23) | 43 (46) | 25 (26) |
| Early moderate-response (%) | 55 (40) | 58 (43) | 40 (41) | 44 (44) | 40 (42) | 38 (39) |
| Early no-response (%) | 16 (12) | 43 (32) | 12 (12) | 33 (33) | 11 (12) | 34 (35) |

**Table 1B** Early EULAR response per treatment strategy for all patients and patients with complete data on long-term outcome.

Number (%) is shown for all categories. $CAMERA_{total}$= all available data on all patients included (ITT population); TC= tight control treatment strategy; CT= conventional treatment strategy; EULAR response is determined at 6 months.

### Treatment strategies and long-term outcome

Figure 1 shows disease activity and joint damage over 5 years for the treatment strategies based on available data.

The mean (SD) DAS28 at 5 years of treatment were 2.68 (1.0) and 2.75 (1.3) for patients in the tight control and conventional strategy, respectively (p=0.66). The median (interquartile range, IQR) radiographic progression rates at 5 years were 1.4 (0.1-3.6) and 0.8 (0.0-3.2), respectively (p=0.50).

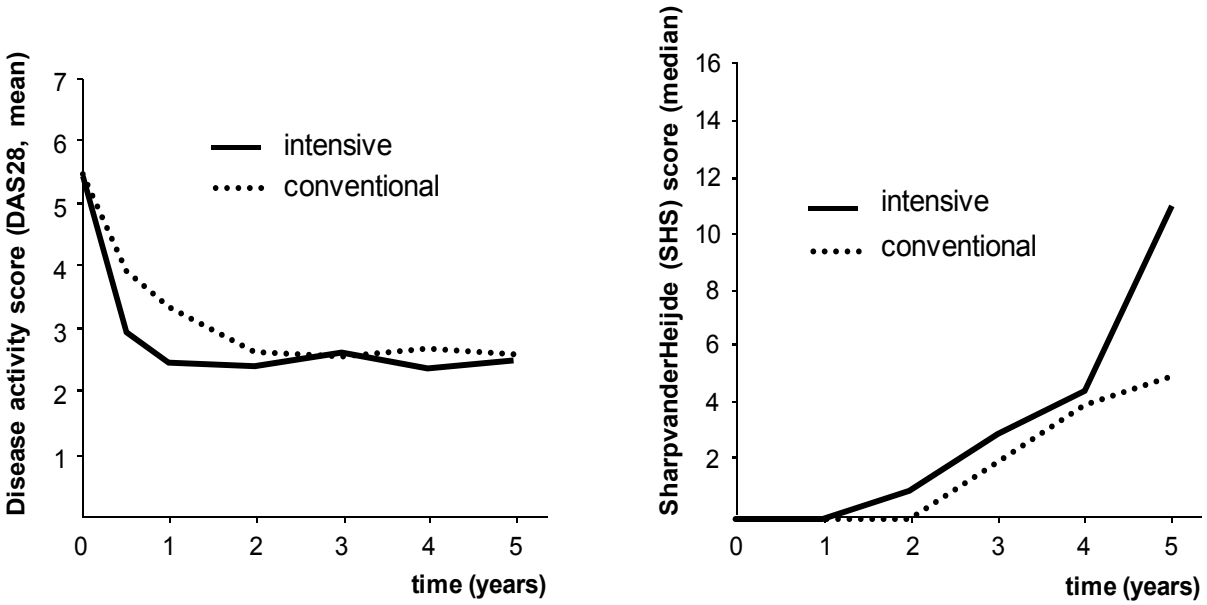


**Figure 1A-B.** Course of disease activity (DAS28, mean values; A) and radiographic joint damage (SHS, median values; B) during 5 years of follow-up for the patients who were (initially) treated intensively (solid lines) or conventionally (dotted lines) according to the CAMERA protocol. There were no statistically significant differences in the courses of disease activity and radiographic progression over 5 years.

**Early response to treatment and long-term outcome**

Figure 2 shows disease activity and joint damage over time for the early good-, moderate- and non-responders based on available data.

Patients with an early good-, moderate- or non-response respectively had a mean (SD) DAS28 at 5 years of 2.39 (1.2), 2.69 (1.1), and 3.11 (1.2). At 5 years, early good-responders had statistically significantly lower disease activity as compared to early moderate- and non-responders (p=0.09 and p=0.001, respectively) and early moderate-responders had statistically significantly lower disease activity compared to early non-responders (p=.046) (Figure 2A). Patients with an early good-, moderate- or non-response had a median (IQR) radiographic progression rate of respectively 0.6 (0.0-2.2), 1.5 (0.2-3.6), and 2.5 (0.5-6.2). The differences between the early good-responders and the early moderate- and non-responders were statistically significant (p=0.013 and p=0.001, respectively), moderate- and non-responders were not statistically significantly different (Figure 2B).

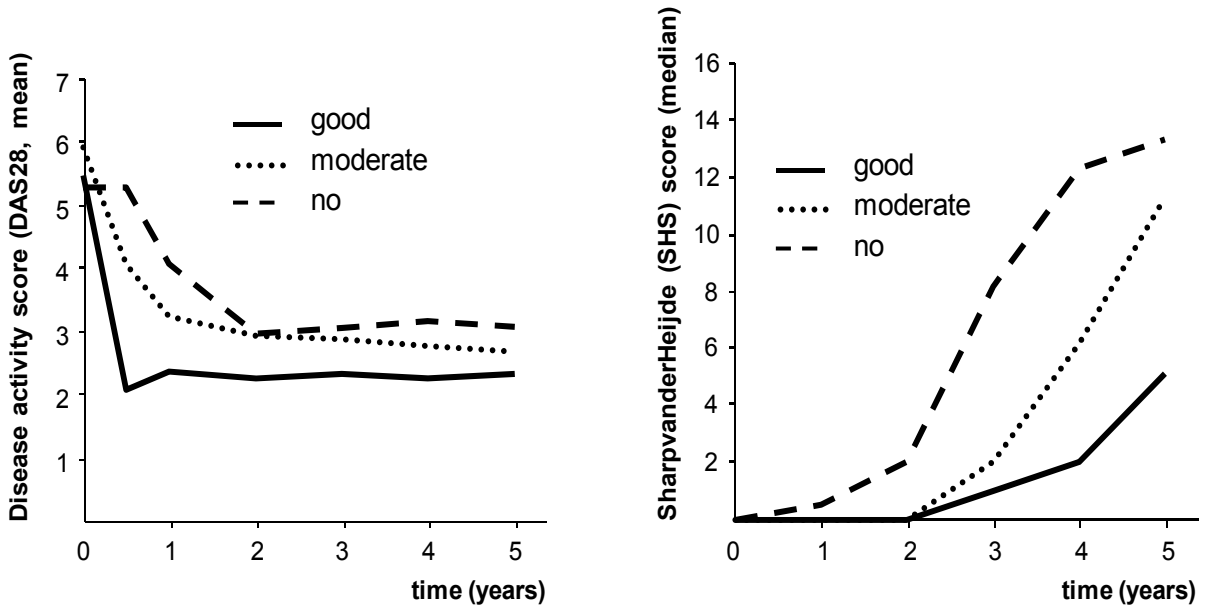


**Figure 2A-B.** Course of disease activity (DAS28, mean values; A) and radiographic joint damage (SHS, median values; B) during 5 years of follow-up for patients who were early good-responders (solid line), early moderate-responders (dotted line), and early non-responders (dashed line); based on EULAR response criteria. Early good-responders showed significantly better results for clinical (p=0.09 and p=0.001) and radiographic (p=0.013 and p=0.001) outcomes over 5 years when compared to early moderate- and non-responders respectively.

In the multiple regression analysis, early response was significantly related to 5-year DAS28, independently of RF-status and baseline disease activity. The R-square of the model increased from 0.037 to 0.091 when including early response (Table 2A). The standardized beta's showed that the influence of EULAR response on outcome was higher compared to the predictive value of RF and baseline DAS28 (Table 2A).

| Item | B | 95%CI | standardised Beta | p | R-square |
|---|---|---|---|---|---|
| Intercept | 1.709 | .517 - 2.901 | | .005 | |
| Age | .006 | -.007 - .018 | .066 | .384 | .001 |
| Gender | .347 | -.031 - .725 | .139 | .071 | .017 |
| Treatment strategy | .174 | -.172 - .519 | .076 | .323 | .017 |
| RF positive | .283 | -.083 - .649 | .113 | .128 | .036 |
| Baseline disease activity | .042 | -.126 - .211 | .039 | .622 | .038 |
| EULAR early good-response* | -.752 | -1.221 - -.284 | -.313 | **.002** | |
| EULAR early moderate-response* | -.427 | -.877 - .023 | -.184 | .063 | .091 |

**Table 2A** Multiple regression analysis with disease activity at 5 years of treatment as dependent outcome.
* Early EULAR non-response used as reference category.
R-square= explained variance. The R-square is shown for every extra variable included in the model.

The early response was also significantly related to the mean yearly radiographic progression rate next to the established predictors RF-status and baseline joint damage.

The R-square of the model increased from 0.208 to 0.242 when including the EULAR early response categories (Table 2B). However, the standardized beta's showed that the influence of EULAR response on outcome was smaller than that of baseline joint damage (Table 2B).

| Item | B | 95%CI | standardized Beta | p | R-square |
|---|---|---|---|---|---|
| Intercept | .968 | .290 - 1.645 | | .005 | |
| Age | -.001 | -.010 - .007 | -.020 | .773 | .000 |
| Gender | -.123 | -.370 - .124 | -.068 | .328 | .008 |
| Treatment strategy | .171 | -.062 - .404 | .102 | .149 | .013 |
| RF positive | .354 | .105 - .603 | .193 | **.006** | .055 |
| Baseline joint damage | .070 | .044 - .095 | .365 | **.000** | .200 |
| EULAR early good-response* | -.427 | -.740 - -.114 | -.246 | **.008** | |
| EULAR early moderate-response* | -.091 | -.329 - .210 | -.054 | .552 | .242 |

**Table 2B** Multiple regression analysis with mean yearly radiographic progression rate over 5 years of treatment as dependent outcome.

* Early EULAR non-response used as reference category.

R-square= explained variance. The R-square is shown for every extra variable included in the model.

To investigate whether early response has a different influence on long-term outcome in the tight control versus the conventional treatment strategy, the interaction between treatment strategy and early response was investigated. In both strategies, early good- and moderate-response were associated with better long-term disease activity when compared to early non-response in the conventional strategy (p=0.010 and p=0.43 for tight control, and p=0.041 and p=0.07 for the conventional strategy, respectively). The influence of early response to treatment was not significantly different between the treatment strategies. However, the moderate- and non-responders in the tight control strategy seemed to have worse outcome and the good-responders seemed to have a slightly better outcome when compared to the same responder groups of the conventional strategy.

Regarding radiographic progression rate also early good- and moderate-responders had better outcomes as compared to non-responders in the tight control as well as in the conventional treatment strategy (p=0.010 and p=0.37 and p<0.0001 and p=0.029, respectively). The influence of the early response to treatment on progression rate was not significantly different between the treatment strategies.

Adding established predictors (RF, baseline disease activity, and baseline joint damage) and the patients' characteristics age and gender to the models did not alter the results above (Table 3A and 3B).

| Item | $B_{uni}$ | 95%CI | $B_{multi}$ | 95%CI |
|---|---|---|---|---|
| Intercept | 3.047 | 2.658 - 3.436 | 1.492 | .255 - 2.730 |
| Age | | | .005 | -.008 - .018 |
| Gender | | | .348 | -.029 - .726 |
| RF positive | | | .306 | -.060 - .672 |
| Baseline disease activity | | | .063 | -.109 - .235 |
| EULAR early good-response TC* | -.676 | -1.188 - -.164 | -.576 | -1.110 - -.042 |
| EULAR early moderate-response TC* | -.211 | -.736 - .315 | -.116 | -.666 - .433 |
| EULAR early no-response TC* | .236 | -.517 - .988 | .658 | -.158 - 1.475 |
| EULAR early good-response CT* | -.634 | -1.241 - -.028 | -.423 | -1.040 - .194 |
| EULAR early moderate-response CT* | -.481 | -.996 - .033 | -.345 | -.877 - .187 |

**Table 3A** Univariate and multivariate regression analyses with disease activity at 5 years as dependent outcome.

* Conventional treated patients with EULAR early non-response were used as reference category (TC= tight control treatment strategy; CT= conventional treatment strategy).

$B_{uni}$= analysis with only categories based on early EULAR response and treatment strategy included; $B_{multi}$= multivariate analysis; including age, gender, rheumatoid factor (positive) and baseline disease activity as covariates

| Item | $B_{uni}$ | 95%CI | $B_{multi}$ | 95%CI |
|---|---|---|---|---|
| Intercept | 1.287 | 1.014 - 1.560 | 1.027 | .334 - 1.720 |
| Age | | | -.001 | -.010 - .007 |
| Gender | | | -.124 | -.372 - .124 |
| RF positive | | | .345 | .095 - .596 |
| Baseline joint damage | | | .068 | .042 - .094 |
| EULAR early good-response TC* | -.482 | -.848 - -.117 | -.263 | -.624 - .098 |
| EULAR early moderate-response TC* | -.170 | -.541 - .202 | .026 | -.343 - .395 |
| EULAR early no-response TC* | -.294 | -.846 - .259 | -.026 | -.565 - .513 |
| EULAR early good-response CT* | -.827 | -1.247 - -.408 | -.545 | -.952 - -.138 |
| EULAR early moderate-response CT* | -.420 | -.796 - -.045 | -.137 | -.509 - .235 |

**Table 3B** Multiple regression analyses with mean yearly radiographic progression rate over 5 years as dependent outcome.

* Conventional treated patients with EULAR early non-response were used as reference category (TC= tight control treatment strategy; CT= conventional treatment strategy).

$B_{uni}$= analysis with only categories based on early EULAR response and treatment strategy included; $B_{multi}$= multivariate analysis; including age, gender, rheumatoid factor (positive) and baseline joint damage as covariates.

Since there was considerable missing data, the possible influence on the results was investigated using multivariate imputation analysis. Prediction models were used to impute missing data on long-term outcome. Models were based on gender, age, RF-status, and DAS28 at baseline, at 6 months and 1 year for the long-term DAS28 and based on gender, age, DAS28 at baseline, radiographic damage at baseline and 1 year for the radiographic progression rate. Using this imputation method, data of 270 patients (139 tight control, 131

conventional strategy) and 282 (143 tight control, 139 conventional strategy) patients was available for analysis regarding long-term disease activity and radiographic progression respectively. The results of the analyses using the imputed dataset were similar to the results using the original (complete case) dataset, both regarding the long-term outcome of the treatment strategies and early response to treatment (data not shown).

## DISCUSSION

The difference in disease activity between the tight control and conventional treatment strategy of CAMERA slightly decreased over the following years and was absent after 5 years. Remarkably, joint damage is still minor and not different between both treatment strategies after this period. When classifying patients according EULAR response at 6 months of treatment, there were clear differences in long-term outcome, in favour of early good-responders. This implies that early response is very important in defining an optimal treatment strategy and optimizing treatment after initial non-response might further improve a treatment strategy in early RA.

A possible explanation for the loss of differences between the strategies after 5 years might be that the tight control principle was abandoned after the study period of 2 years. Medication then was free and less frequent visits and less tight regulation of disease activity generally were applied, among others due to logistic reasons. Patients in the tight control strategy arm might have been treated less tightly after two years and those in the conventional strategy arm more tightly after 2 years, diluting the difference in effect. To prove that using the tight control principle over a longer period is beneficial, trials applying tight control over longer periods of time are needed. Also the subsequent drug-intensivation steps in case of insufficient MTX response as defined in the CAMERA protocol (i.e. scMTX and cyclosporine) in the first two years might not be sufficiently effective [20] in reaching remission in the short term. Maybe an intensivation of the drug-strategy protocol including biologicals early in the disease would improve these long-term outcomes.

When comparing the follow-up of CAMERA to other tight control strategies similar disease activity values were seen. When comparing with the FIN-RACo study;[21] the tight control groups had a mean DAS28 of 2.68 in CAMERA and around 2.5 in FIN-RACo after 5 years of treatment, this was respectively 2.75 and around 3.0 for the non-tight control groups. In another tight control study (BeSt), 42 - 51% of patients were in clinical remission (defined by DAS <1.6) at 5 years of treatment depending on strategy arm;[22] this was 57% at 5 years (defined by DAS28 <2.6) for all available patients in CAMERA.

The differences in clinical outcome between early response to treatment was still evident after 5 years, in contrast to the effect of the treatment strategies. This indicates that an early response to treatment is a good predictor for long-term outcome; furthermore it was independent of known predictors for the long-term outcome of RA patients. The early response to treatment is also influenced by treatment strategy, dictating the frequency of medication changes according to study protocol. So, early non-responders in the tight

control strategy might be 'real' non-responders whereas the non-responder subgroup in the conventional treatment strategy might be composed of non-responders and 'late-responders'. The results of multiple regression analyses of early response to treatment are compatible with this hypothesis: patients in the conventional treatment strategy with an early moderate- or non-response were slightly better off when compared to the respectively moderate- or non-response patients of the tight control strategy (see Table 3A and 3B).
In all, our results suggest that with tight control, patients who do not have an early good-response to treatment after 6 months, should already at that time and possibly even earlier switch to another strategy or medication scheme. This is in accordance to guidelines in a recent position paper on treatment of RA.[23]
Limitations of this study are that only 2/3 of the patients were available for analysis after 5 years of treatment. However, there seemed to be no selective drop-out and also after multivariate imputation no significant or relevant differences in results were found. This suggests that the available patients were a good representation of the total CAMERA population. Another limitation is that the early response to treatment was determined after 6 months of treatment. This time period was chosen to allow for a relevant period to optimize MTX treatment for the conventional treatment group (with only three-monthly visits). However, for patients in the tight control strategy (with monthly visits), this time period might have been set already earlier; e.g. after 3 months of treatment. Preferably, the response to treatment should be identified as early as possible in the disease course.
Although tight control was effective in the 2-year trial, the effectiveness fades during follow-up, when the tight control principle is no longer maintained strictly. The tight control principle will probably be used more frequently in the near future, according to recently published recommendations for daily clinical practice.[23] One of the recommendations is that patients with high or moderate disease activity should be monitored frequently (i.e. monthly), whereas patients with sustained low disease activity or remission could be monitored less frequently, but still every 3 to 6 months. This implies that in patients with persisting moderate or high disease activity indeed the tight control strategy could and should be continued.
In conclusion, no differences in disease activity and progression of joint damage were seen anymore between the treatment strategies of CAMERA after 5 years of treatment. In contrast, an early good-response to treatment (determined at 6 months) is an independent predictor of better long-term outcome, irrespective of the treatment strategy used. These data suggest the continuing use of the tight control principle over time and the use of more adequate medication in moderate- and non-responders early in the disease.

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## REFERENCES


1. Boers M. Understanding the window of opportunity concept in early rheumatoid arthritis. Arthritis Rheum 2003;48:1771-4.
2. Bakker MF, Jacobs JW, Verstappen SM, et al. Tight control in the treatment of rheumatoid arthritis: efficacy and feasibility. Ann Rheum Dis 2007;66 Suppl 3:iii56-60.
3. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. Arthritis Rheum 2005;52:3381-90.
4. Grigor C, Capell H, Stirling A, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. Lancet 2004;364:263-9.
5. Mottonen T, Hannonen P, Leirisalo-Repo M, et al. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. Lancet 1999;353:1568-73.
6. Vazquez I, Graell E, Gratacos J, et al. Prognostic markers of clinical remission in early rheumatoid arthritis after two years of DMARDs in a clinical setting. Clin Exp Rheumatol 2007;25:231-8.
7. Bansback N, Young A, Brennan A, et al. A prognostic model for functional outcome in early rheumatoid arthritis. J Rheumatol 2006;33:1503-10.
8. Machold KP, Stamm TA, Nell VP, et al. Very recent onset rheumatoid arthritis: clinical and serological patient characteristics associated with radiographic progression over the first years of disease. Rheumatology (Oxford) 2007;46:342-9.
9. van der Heide A, Remme CA, Hofman DM, et al. Prediction of progression of radiologic damage in newly diagnosed rheumatoid arthritis. Arthritis Rheum 1995;38:1466-74.
10. Verstappen SM, van Albada-Kuipers GA, Bijlsma JW, et al. A good response to early DMARD treatment of patients with rheumatoid arthritis in the first year predicts remission during follow up. Ann Rheum Dis 2005;64:38-43.
11. Wessels JA, van der Kooij SM, le Cessie S, et al. A clinical pharmacogenetic model to predict the efficacy of methotrexate monotherapy in recent-onset rheumatoid arthritis. Arthritis Rheum 2007;56:1765-75.
12. Aletaha D, Funovits J, Keystone EC, et al. Disease activity early in the course of treatment predicts response to therapy after one year in rheumatoid arthritis patients. Arthritis Rheum 2007;56:3226-35.
13. Nell VP, Machold KP, Eberl G, et al. Benefit of very early referral and very early therapy with disease-modifying anti-rheumatic drugs in patients with early rheumatoid arthritis. Rheumatology (Oxford) 2004;43:906-14.
14. Smolen JS, van der Heijde DM, St Clair EW, et al. Predictors of joint damage in patients with early rheumatoid arthritis treated with high-dose methotrexate with or without concomitant infliximab: results from the ASPIRE trial. Arthritis Rheum 2006;54:702-10.
15. Verstappen SM, Jacobs JW, van der Veen MJ, et al. Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open label trial). Ann Rheum Dis 2007;66:1443-9.
16. 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.
17. van Gestel AM, Prevoo ML, van 't Hof MA, et al. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism Criteria. Arthritis Rheum 1996;39:34-40.
18. Prevoo ML, van 't Hof MA, Kuper HH, et al. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38:44-8.
19. van der Heijde DM, van Riel PL, Nuver-Zwart IH, et al. Effects of hydroxychloroquine and sulphasalazine on progression of joint damage in rheumatoid arthritis. Lancet 1989;1:1036-8.
20. Bakker MF, Jacobs JWG, Welsing PMJ, et al. Are switches from oral to subcutaneous MTX or addition of cyclosporine to MTX useful steps in a tight control treatment strategy for RA? A post-hoc analysis of the CAMERA study. Ann Rheum Dis 2010;69:1849-52.

21. Rantalaiho V, Korpela M, Hannonen P, et al. The good initial response to therapy with a combination of traditional disease-modifying antirheumatic drugs is sustained over time: the eleven-year results of the Finnish rheumatoid arthritis combination therapy trial. Arthritis Rheum 2009;60:1222-31.
22. Klarenbeek NB, Allaart CF, Kerstens PJ, et al. The BeSt story: on strategy trials in rheumatoid arthritis. Curr Opin Rheumatol 2009;21:291-8.
23. Smolen JS, Aletaha D, Bijlsma JW, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis 2010;69:631-7.

Chapter 6

# Low-dose prednisone inclusion into a MTX-based tight control strategy for early rheumatoid arthritis: better control of disease and erosive joint damage. Results from the double-blind randomized CAMERA-II trial.

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## ABSTRACT

### Objective

Tight control treatment strategies for early rheumatoid arthritis (RA) are highly effective, but leave room for improvement. It is investigated whether including 10 mg/day prednisone from the start of treatment to a methotrexate (MTX) based tight control strategy increases its effectiveness.

### Methods

Patients with early RA (<1 year) were enrolled in a two-year prospective randomized, placebo-controlled, double-blind, multi-centre trial called CAMERA-II (Computer Assisted Management in Early RA-II). Patients were randomized to the MTX-based tight control strategy with either prednisone (MTX-pred) or placebo (MTX-plac). MTX treatment was tailored to the individual patient at monthly visits, based on predefined response criteria aiming for remission. Primary endpoint was radiographic erosive joint damage after two years. Secondary endpoints included response criteria, remission, and the use of biologicals.

### Results

Respectively 117 and 119 patients were randomized to MTX-pred and MTX-plac. Erosive joint damage was less in the MTX-pred than in the MTX-plac group (median (IQR); 0 (0-0) vs. 0 (0-2), p=0.04). The strategy with MTX-pred was also more effective in reducing disease activity and disability ($p \leq 0.03$). A higher proportion of patients in the MTX-pred group achieved sustained remission (72% vs. 61%, p=0.09) and a lower proportion needed biological treatment (14% vs. 36%, $p<0.001$), compared to MTX-plac. Fewer patients in the MTX-pred group experienced adverse events compared to MTX-plac (29% vs. 35%).

### Conclusions

Inclusion of low-dose prednisone into a MTX-based tight control treatment strategy in early RA increases effectiveness and outcome yet does not increase toxicity. It decreases the need for (early) treatment with biologicals.

## INTRODUCTION

Rheumatoid arthritis (RA) is preferentially treated as soon as possible after diagnosis, when the disease is believed to be most responsive to treatment, in the so called 'window of opportunity'.[1-4] Both short-term and long-term prognosis are better if remission (i.e. absence of symptoms and signs) is induced early in the disease course.[5, 6] This can be achieved using 'tight control' treatment strategies,[7-9] tailored to the disease activity of an individual RA patient with dose and medication adjustments, and aimed at a predefined level of low disease activity, preferably remission ("treat to target"), within a limited period of time.[8] Both step-down strategies (starting with combination treatment with disease modifying anti-rheumatic drugs (DMARDs), tapering down in case of clinical response)[6, 10] and step-up strategies (starting one DMARD and adding DMARDs in case of insufficient effect) have been shown to be effective.[11] Step-down strategies benefit optimally from the 'window of opportunity' with quick symptom relief for patients, but may potentially result in overtreatment. In contrast, in step-up strategies medication can be tailored to disease activity of the individual patient without overtreatment; however the 'window of opportunity' period may be used less efficiently and symptom relief may be slower compared to step-down treatment.[12]

Methotrexate (MTX) is the most commonly used and most effective conventional DMARD for RA (anchor drug). It is cheap, effective, relatively fast acting and well tolerated; it also slows down joint damage, and can be administered orally and subcutaneously in a relatively wide dose range (2.5-30 mg/wk).[13-16]

The previous CAMERA (Computer Assisted Management in Early Rheumatoid Arthritis) study applied MTX in a step-up tight control strategy;[17] increased effectiveness compared to a usual care strategy with MTX was shown. In the tight control group 50% experienced at least one period of remission compared to 37% in usual care group. In an earlier Utrecht randomized clinical trial, prednisone 10 mg/day in early RA patients showed inhibition of radiographic joint damage.[18] From this result and that of other studies it was concluded that prednisone is a DMARD.[19] Glucocorticoids inhibit amongst others the cytokine-induced production of the ligand for receptor activator for nuclear factor κB, which activates osteoclasts.[20] This explains why prednisone particularly reduces the formation of bone erosions.[21]

Based on these findings, we hypothesized that addition of prednisone to a MTX-based tight control strategy from the start of treatment of early RA could be more effective than the same strategy without prednisone, regarding disease activity and radiographic outcome, i.e. erosive joint damage.

## PATIENTS AND METHODS

From 2003 until 2008, early RA patients who fulfilled the 1987 revised American College of Rheumatology (ACR) criteria for RA[22] were eligible for this randomized, placebo-

controlled, double-blind, prospective, multi-centre, two-year tight control strategy trial: CAMERA-II. The medical research ethics committee of all hospitals involved approved the study (clinical trial registration number ISRCTN70365169). All consecutive patients who visited the outpatient clinic of one of the 7 rheumatology departments in the region of Utrecht, the Netherlands, collaborating in the Utrecht Early Rheumatoid Arthritis Cohort study group, were asked to participate and patients gave written informed consent before entering the study.
Inclusion criteria were disease duration <1 year, age >18 years, and a DMARD- and glucocorticoid-naïve status. Exclusion criteria were: Cockcroft creatine clearance <75 ml/min, liver enzymes ASAT/ALAT >2*upper limit of normal; ULN), active or recent hepatitis or liver cirrhosis, malignancies, inadequately controlled diabetes mellitus or arterial hypertension, serious infections, serious cardiac and/or respiratory diseases, leucopenia and/or thrombocytopenia, inadequate anti-conception, pregnancy and/or breast feeding, osteoporosis, use of cytotoxic or immunosuppressive drugs within a period of three months before inclusion, current or past substance of alcohol use >2 units/day, and psychological problems or intellectual disorders which would make adherence to the study protocol impossible.

**Treatment strategies**
Randomization to tight control MTX-based treatment strategy in combination with either low-dose prednisone (MTX-pred; 10 mg/day) or placebo (MTX-plac) in blocks of 4 patients stratified for each clinic was performed by the pharmacy of the University Medical Center Utrecht (UMCU). Unblinding was done at the end of the study by the pharmacy of UMCU, or in an earlier phase of the study in case of dropout due to severe adverse events (SAEs) or surgery if glucocorticoid stress schemes were needed.
All patients received bisphosphonates (alendronate or risedronate), and calcium carbonate preparations with vitamin D (cholecalciferol). Use of nonsteroidal anti-inflammatory drugs (NSAIDs) was allowed, but intra-articular injections were avoided as much as possible and recorded.
The tight control MTX-based treatment strategy comprised of a start with 10 mg/wk oral MTX with daily folic acid (0.5 mg each day, except for the day of MTX intake). At each monthly visit the swollen joint count (SJC), tender joint count (TJC), erythrocyte sedimentation rate (ESR), and visual analogue scale (VAS, 0-100 mm; 100=worst) for general well-being were assessed and entered in a computer decision program by the rheumatologist. The program calculated whether or not predefined criteria of response (>20% improvement compared to previous visit in SJC and two out of following three: TJC, ESR, and VAS) were met.[17] At each visit, if criteria of response were not met, the dosage of MTX was increased by 5 mg/wk until remission (SJC=0 and two out of three: TJC ≤3, VAS ≤20 mm, ESR ≤20 mm/h$^{1st}$), the maximum dose of 30 mg/wk MTX or the maximum tolerable dose was reached.[17] If patients did not meet the predefined goal of remission after reaching the maximum (tolerable) dose, MTX was administered subcutaneously

(scMTX) and subsequently cyclosporine was added as next strategy steps, according to protocol.[17] Shortly after starting the trial (after about 20% of inclusions) a protocol amendment was made replacing cyclosporine by adalimumab as next step, added to the maximum scMTX dose. The starting dose of adalimumab was 40 mg subcutaneously every 2 weeks; if the criteria of response were not met after 12 weeks the dose was increased to 40 mg/week. In case of sustained remission during at least 4 subsequent visits, if applicable, adalimumab dose was reduced to 40 mg every 2 weeks and thereafter MTX was reduced stepwise with 2.5 mg/wk each month as long as remission was present; if remission was lost, the dose of MTX was increased again in steps of 5 mg/wk.[17]
If oral MTX was not tolerated, patients switched to scMTX (same dose and escalation scheme as used orally) and thereafter the protocol was followed as described above. In case of predefined adverse events (AEs) with oral MTX use (e.g. leukocyte count ≤2.5x$10^9$/l, thrombocyte count ≤100x$10^9$/l), the scMTX step was skipped and cyclosporine/adalimumab was added to the maximum (tolerable) dose of oral MTX.

**Clinical variables**
At baseline and subsequent monthly visits, the following disease activity variables were assessed: SJC (0-38 joints), TJC (0-38 joints), VAS pain (mean score of VAS pain at night and in the morning, 0-100 mm; 100=worst possible pain), VAS general well-being (0-100 mm; 100=worst score), ESR (mm/$h^{1st}$), C-reactive protein (CRP, mg/l), and duration of morning stiffness (0-180 minutes). Disease activity score (DAS28) was calculated,[23] which is an index for disease activity based on TJC and SJC of 28 joints, ESR, and VAS general well-being. The Health Assessment Questionnaire (HAQ, Dutch version[24]), measuring physical disability, was assessed every three months. Rheumatoid factor status at baseline was recorded as positive or negative. Screening at baseline included serum albumin, hepatitis B surface antigen (HbsAg) and anti-hepatitis C virus (HCV), serum and urine glucose, x-rays of chest, thoracic and lumbar spine, and bone densitometry. Radiographs of hands and feet were taken at inclusion and annually thereafter.

**Primary endpoint**
The primary endpoint was erosive radiographic joint damage at two years. Radiographs were scored in chronological order according to the SharpvanderHeijde score (SHS, range 0-448), comprising scores for erosions and joint space narrowing (JSN) by two readers who were blinded for patient characteristics and treatment strategy.[25] In case of disagreement, the final scores were based on consensus between the two observers.

**Secondary endpoints**
Secondary endpoint measures were the number of patients satisfying the ACR and EULAR response criteria at one and two years, number of patients in sustained remission (defined above) at any time during the trial, duration of remission, time until first remission, individual

disease activity variables over time, and the number of patients who needed the scMTX and/or cyclosporine/adalimumab strategy steps during the trial.

**Adverse events**

Predefined adverse events (AEs) were evaluated and recorded at every visit according to protocol. These included abnormal liver enzyme test results (>ULN), anaemia (Hb <6.5 mmol/l), leucopenia (<3.5*$10^6$/l), thrombocytopenia (<150*$10^6$/l), pancytopenia (leucocytes ≤2.5*$10^6$/l, and trombocytes ≤100*$10^6$/l), renal dysfunction (serum creatinine >ULN), and pneumonitis.

**Statistical analyses**

Intention-to-treat analyses were performed. For radiographic joint damage, missing data were imputed by assuming a constant progression rate or, if this was not possible, with multivariate imputation analysis based on patients with complete data. For missing data on disease activity variables the average value was calculated from the adjacent visits, in case of last available data point in time, this value was carried forward. Patients who dropped out were considered non-responders for the calculation of the ACR and EULAR response criteria.

Differences between the 2 groups in means of continuous data were tested with independent t-tests or Mann Whitney-U tests, where appropriate, and differences in categorical data with Chi-square tests. The difference in duration and time until sustained remission between the 2 groups was tested with log-rank tests. Differences in disease activity variables between the 2 groups over time were tested using longitudinal regression analyses (mixed model) with treatment strategy and time as independent variables and the disease activity variable (with separate analyses for each individual variable) as dependent variable.

The statistical software SPSS 15.0 and SAS 9.1 were used for analyses of data. A p value <0.05 was considered to be statistically significant.

**RESULTS**

Table 1 shows no significant differences in baseline characteristics between the 2 groups, in total 236 patients. During the study, 32 patients in the MTX-pred group and 34 patients in the MTX-plac group withdrew due to various reasons (see Figure 1); 85 patients in each arm completed the 2 year trial.

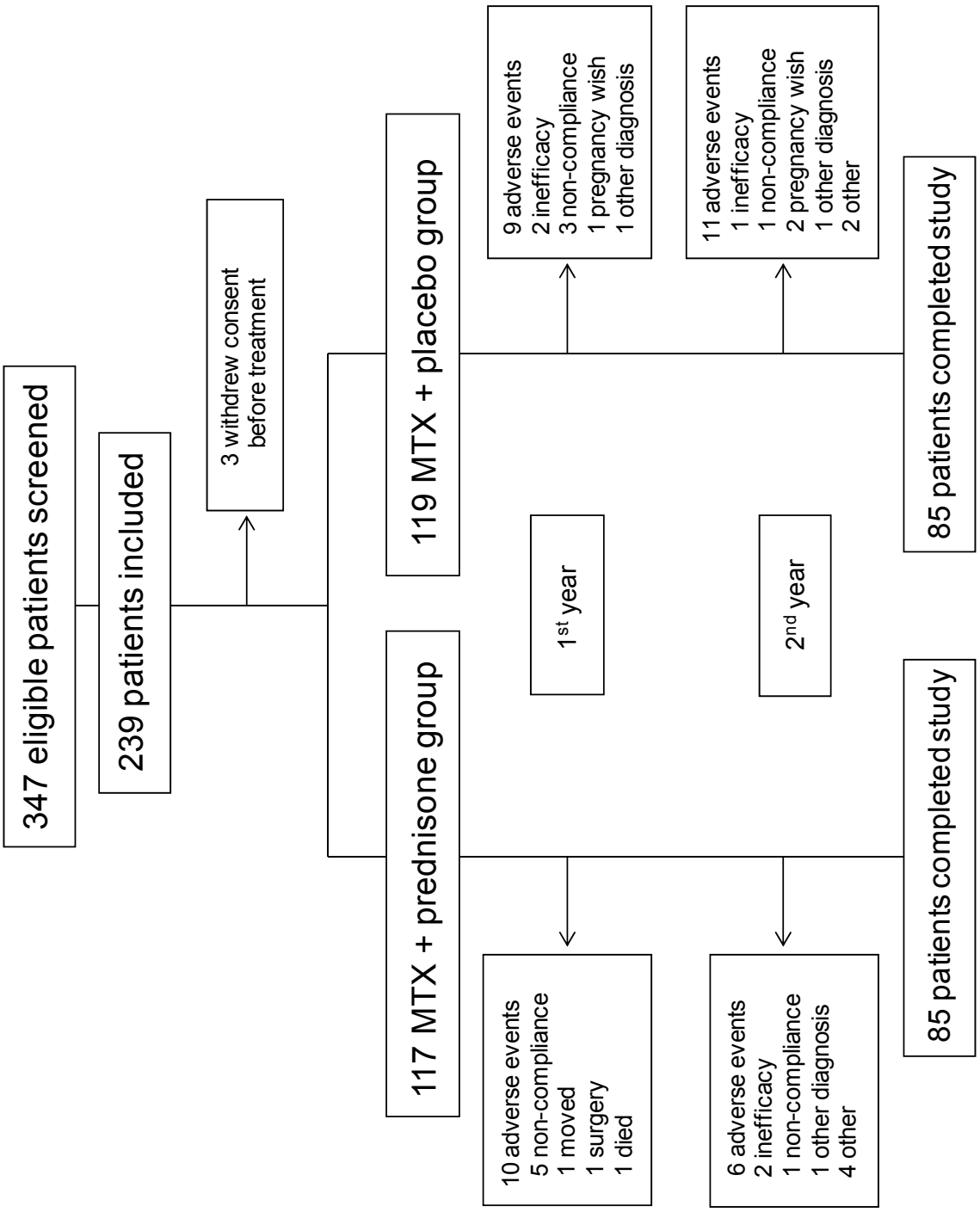


**Figure 1** Flowchart of the CAMERA-II trial.

| Characteristic | MTX + PRED n = 117 | MTX + PLAC n = 119 |
|---|---|---|
| | **n (%)** | **n (%)** |
| Female gender | 70 (60) | 72 (61) |
| RF positive | 64 (55) | 73 (61) |
| Radiographic damage present | 34 (29) | 24 (20) |
| Erosions present | 20 (17) | 14 (12) |
| JSN present | 25 (21) | 21 (18) |
| | **mean (SD)** | **mean (SD)** |
| Age (years) | 54 (14) | 53 (13) |
| Morning stiffness (min) | 87 (53) | 87 (60) |
| VAS general (mm) | 58 (22) | 56 (22) |
| VAS pain (mm) | 49 (26) | 49 (25) |
| TJC | 17 (9) | 15 (9) |
| SJC | 15 (9) | 14 (8) |
| HAQ | 1.0 (0.7) | 1.2 (0.6) |
| DAS28 | 5.8 (1.3) | 5.5 (1.1) |
| ESR (mm/h$^{1st}$) | 36 (25) | 34 (24) |
| CRP (mg/l) | 31 (35) | 24 (27) |
| | **median (IQR)** | **median (IQR)** |
| SHS - total | 0 (0-1) | 0 (0-0) |
| SHS - erosions | 0 (0-0) | 0 (0-0) |
| SHS - JSN | 0 (0-0) | 0 (0-0) |

**Table 1** Baseline demographic and clinical characteristics of all patients in the CAMERA-II trial. MTX+PRED= methotrexate based tight control strategy combined with prednisone; MTX+PLAC= methotrexate based tight control strategy with placebo; IQR: interquartile range; RF= rheumatoid factor, JSN= joint space narrowing; ESR= erythrocyte sedimentation rate; CRP= C-reactive protein; VAS= visual analogue scale; TJC= tender joint count, based on 38 joints; SJC= swollen joint count, based on 38 joints; HAQ= Health Assessment Questionnaire; DAS28= disease activity score based on joint counts of 28 joints; SHS= SharpvanderHeijde radiographic score.

### Primary endpoint measurement

The median (interquartile range, IQR) erosion score at 2 years and the mean (SD) progression rate of the erosion score after 2 years differed statistically significantly (0 (0-0) vs. 0 (0-2); p=0.04 and 0.2 (0.9) vs. 0.5 (1.1); p=0.02, respectively) in favour of the MTX-pred group. The cumulative probability plot on erosion scores at 2 years (Figure 2A) shows that 80% of all patients in the MTX-pred group versus 70% in the MTX-plac group were still erosion free and that erosion scores of those with erosions were higher in MTX-plac group. The mean absolute erosion scores (although skewed) over time are shown in Figure 2B.

The total SHS and JSN score at 2 years were not statistically significantly different, nor were the SHS progression rates. The median SHS at 2 years in the MTX-pred group and the MTX-plac group were 0 (0-3) vs. 0 (0-4), p=0.53; the SHS progression rates after 2 years of treatment were 0.5 (1.3) vs. 1.0 (2.6), p=0.14, respectively.

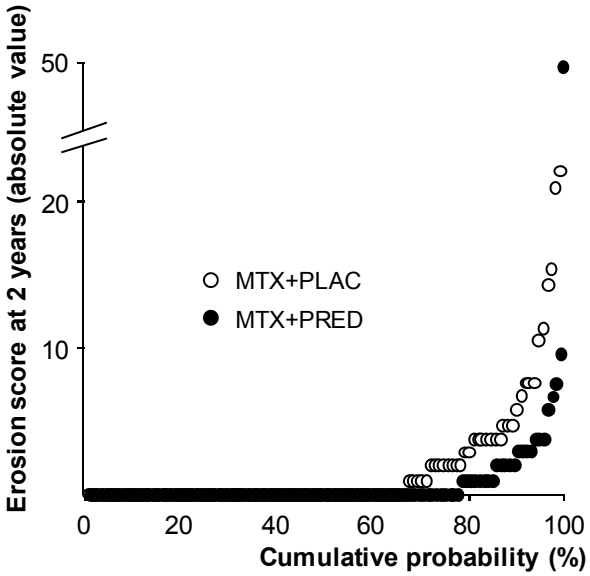


**Figure 2A.** Cumulative probability plot of total erosion score after 2 years of treatment. Black dots for methotrexate combined with prednisone; open circles for methotrexate with placebo.

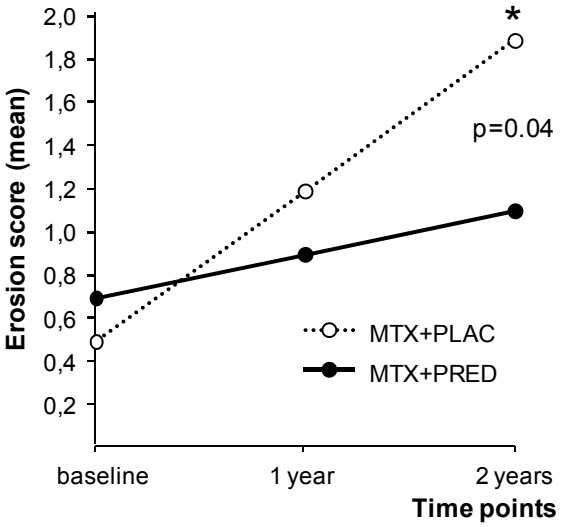


**Figure 2B.** Absolute mean erosion score (although skewed) during the trial. The solid line with black dots for methotrexate combined with prednisone; the dotted line with open circles for methotrexate with placebo. * indicates statistically significant difference between both treatment strategies.

**Secondary endpoint measurements**

The ACR20, ACR50, and ACR70 response rates after one year of treatment for MTX-pred and MTX-plac groups were 70% vs. 66%, 56% vs. 43%, and 27% vs. 26%, respectively; the ACR50 response was statistically different (p=0.04) between the groups in favour of the MTX-pred group. Similar differences were seen after 2 years; ACR20, ACR50, and ACR70 responses 65% vs. 61%, 53% vs. 42%, and 38% vs. 19%; for ACR70, p=0.002. Although similar results for the EULAR response criteria were seen, statistical significance was not reached.

There was a trend towards a higher number of patients who had at least one period of sustained remission in the MTX-pred group: 84 (72%) vs. 73 (61%), p=0.09. Patients in both groups were on average 10 (6) months in remission. However, time until the first sustained remission period was shorter in the MTX-pred group compared to the MTX-plac group: 6 (5) vs. 11 (5) months (p<0.001).

Disease activity variables after 2 years treatment improved on average more in the MTX-pred group compared to the MTX-plac group. The course of the variables DAS28, ESR, VAS pain, and HAQ during the trial is shown in Figure 3A-D. Improvement occurred more rapidly in the MTX-pred group, but the differences observed in the first months tend to diminish: morning stiffness after 3 months, VAS pain and VAS general well-being after 6, CRP and TJC after 10, ESR after 21, SJC after 22, and DAS28 and HAQ after 24 months of treatment. When analyzed over time using longitudinal regression analyses, MTX-pred

performed statistically significantly better on all disease activity variables except for VAS pain (p=0.07) and morning stiffness (p=0.66).
In the MTX-pred group the scMTX strategy step needed to be given to 26 (22%) patients compared to 60 (50%) patients in the MTX-plac group (p<0.001). In the MTX-pred group 18 patients versus 49 patients in the MTX-plac group also needed the subsequent treatment strategy step: 2 (2%) and 7 (6%) patients needed cyclosporine (before the protocol amendment) added to MTX and 16 (14%) and 42 (36%) adalimumab (p<0.001), respectively.

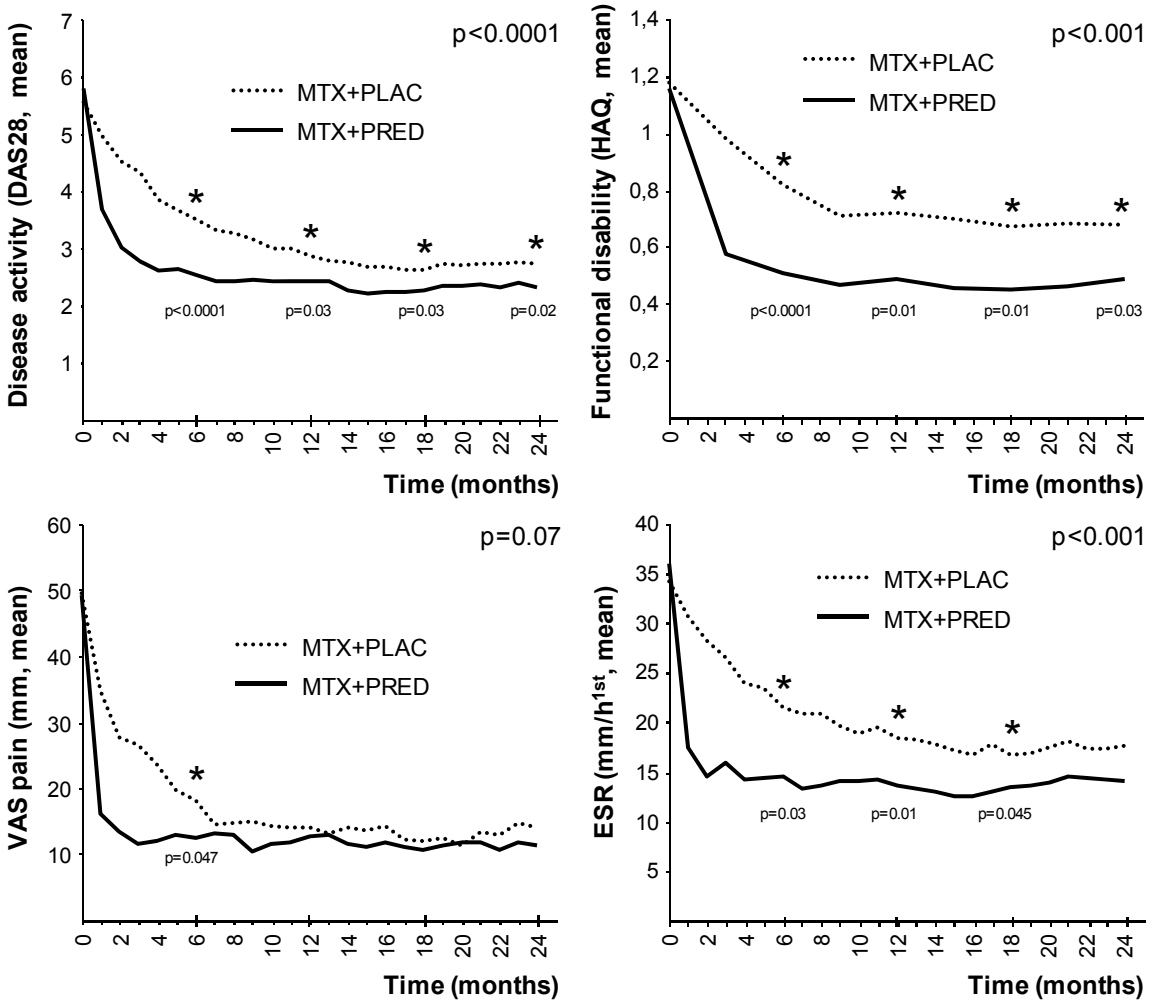


**Figure 3A-D.** Course of clinical variables (mean, SD) during 2 years of treatment. Solid lines for methotrexate combined with prednisone; dotted lines for methotrexate with placebo. p-values (shown in upper right corner) are based on differences between both treatment strategies evaluated with longitudinal regression analyses. * indicate statistically significant differences between both treatment strategies at 6 months, 1 year, 18 months, and 2 years of treatment.

**Adverse events**

At 725 of all 2538 visits (29%) at least one AE was recorded in MTX-pred group versus 950 of all 2682 visits (35%) in MTX-plac group (p<0.001). Most AEs occurred during the first year in both treatment strategies (respectively 468 in MTX-pred group and 589 in MTX-plac group). The nature of AEs and the percentage of AEs in both strategies are shown in detail in Table 2. Most frequent AEs were related to the central nervous system, e.g. headache and dizziness (35% of all AEs in the MTX-pred group and 29% of all AEs in the MTX-plac group), gastrointestinal adverse effects (22% and 26%), and mucocutaneous problems (18% and 18%).

Non-fasting serum glucose values after 2 years were on average 5.7 (1.4) mmol/l in the MTX-pred group and 5.6 (1.5) mmol/l in the MTX-plac group (p=0.55); 13 (11%) in MTX-pred group vs. 9 (8%) in MTX-plac group had higher (>1.0 mmol/l) glucose values compared to baseline. In both groups, 1 patient developed diabetes, see Table 2. On average, patients in the MTX-pred group gained 2.9 (4.2) kilogram in weight during the 2 years compared to baseline; this was 1.3 (5.3) for the MTX-plac group (p=0.03).

## DISCUSSION

Inclusion of prednisone 10 mg/day into a MTX-based tight control strategy enhances clinical efficacy and further slows down erosive joint damage. Patients attained a state of sustained remission at an earlier time point during treatment. In addition, the need for additional treatment steps (i.e. scMTX and subsequently cyclosporine/adalimumab) in the MTX-pred group was only 40% of that in the MTX-plac group.

In line with earlier observations,[19] prednisone predominantly inhibited radiographic erosion score and less JSN and thus total SHS. The direct and indirect effects of glucocorticoids on osteoclastogenesis and bone resorption could account for this discrepancy.[26] This positive effect on erosions was reflected in persistent differences between the groups regarding HAQ scores. Improvements in some disease activity variables were less persistent; partly due to the intensified step-up treatment in the MTX-plac group. Nonetheless, the clear difference in need for additional treatment steps in the MTX-plac group was also a noticeable outcome of this study. The results from the present study support the implementation of a tight control rapid step-up strategy with MTX plus low-dose prednisone and the radiographic results support the concept of a ‘window of opportunity’ in early RA. In this respect, our data corroborate the recent published EULAR guidelines on treatment of RA.[4]

The reduced need for additional treatments, notably biologicals, will have a clear impact on cost-effectiveness.[27-29] A recent published EULAR paper about economic aspects of treatment options in RA supports the concept of an early start of traditional DMARDs and rapid treatment escalation if response is insufficient, rather than starting with biologicals.[29]

| Serious adverse event | MTX + PRED n = 2 | MTX + PLAC n = 5 |
|---|---|---|
| Died | 1 (50) | 0 (0) |
| Hospitalization | 1 (50) | 5 (100) |
| **Adverse event** | **n = 725** | **n = 950** |
| CNS | 254 (35) | 278 (29) |
| Headache | 60 (24) | 67 (24) |
| Dizziness | 51 (20) | 45 (16) |
| Blurred vision | 34 (13) | 30 (11) |
| Dry eyes | 24 (9) | 13 (5) |
| Cataract | 1 (0.4) | 0 (0) |
| Glaucoma | 0 (0) | 0 (0) |
| Gastrointestinal | 163 (22) | 248 (26) |
| Nausea | 51 (31) | 152 (61) |
| Diarrhoea | 18 (11) | 16 (7) |
| Stomach ache | 14 (9) | 17 (7) |
| Mucocutaneous | 127 (18) | 174 (18) |
| Hair loss | 41 (32) | 60 (35) |
| Mouth ulcers | 15 (12) | 35 (20) |
| Itch | 18 (14) | 24 (14) |
| Ulcers | 0 (0) | 0 (0) |
| Liver toxicity | 49 (6.8) | 133 (14) |
| ALAT (>ULN)* | 30 (61) | 87 (65) |
| ASAT (>ULN)* | 16 (33) | 38 (29) |
| φ-GT (>ULN) | 3 (6) | 6 (4) |
| AF (>ULN) | 0 (0) | 2 (2) |
| Pulmonary | 47 (6.5) | 30 (3.2) |
| Cough | 33 (70) | 23 (77) |
| Pneumonitis | 1 (2) | 0 (0) |
| Renal | 15 (2) | 5 (0.5) |
| Creatin increase (>ULN) | 15 (100) | 3 (60) |
| Infections | 6 (0.8) | 7 (1) |
| Antibiotics needed | 1 (17) | 0 (0) |
| Bone | 2 (0.3) | 0 (0) |
| Peripheral fractures | 1 (50) | 0 (0) |
| Haematology | 0 (0) | 2 (0.2) |
| Leucopenia | 0 (0) | 1 (50) |
| Thrombocytopenia | 0 (0) | 1 (50) |
| Anaemia | 0 (0) | 0 (0) |
| Pancytopenia | 0 (0) | 0 (0) |
| Hypertension ** | 11 (1.5) | 18 (2) |
| Diabetes Mellitus *** | 1 (0.1) | 1 (0.1) |
| Other | 50 (7) | 54 (6) |

**Table 2** Adverse events during the trial.

* Combination of ALAT and ASAT during the same visit was present in 15 patients of the MTX+PRED strategy and in 36 patients of the MTX+PLAC strategy.

** Newly developed Diabetes Mellitus based on non-fasting glucose values >11.0 mmol/l.

*** Newly developed hypertension was based on systole >140 mmHg and/or diastole >90 mmHg.

Number of visits with specific type of adverse event (% of total number of adverse events) is shown. A subdivision is made for the most occurring adverse events within each type of event (% of total number within type of adverse event is shown). MTX+PRED= methotrexate combined with prednisone strategy; MTX+PLAC= methotrexate with placebo strategy; CNS= central nervous system; ULN= upper limit of normal.

Our results suggest that use of MTX and prednisone in a tight control strategy could be more cost-effective when compared to starting directly with a biological. A recent meta-analysis showing that combination treatment with DMARDs and glucocorticoids might be just as effective in reducing joint destruction as the combination of biologicals with MTX, although the number of studies was small,[30] supports our results. They enable clinicians in developing countries where biologicals are less available to apply tight control strategies.
Prednisone 10 mg/day can be considered as a low to moderate dose and is related to low risks of AEs in RA patients.[31] Surprisingly, the number of predefined AEs was slightly higher in the MTX-plac group. A possible explanation for this might be more intensive use of NSAIDs in the former group.[32]
In conclusion, the combination of low-dose prednisone and a tight control MTX-based treatment strategy in early RA increases both effectiveness (i.e. disease activity variables) and outcome (i.e. erosive joint damage) without increasing toxicity over 2 years.

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## REFERENCES


1. Boers M. Understanding the window of opportunity concept in early rheumatoid arthritis. Arthritis Rheum 2003;48:1771-4.
2. Knevel R, Schoels M, Huizinga TW, et al. Current evidence for a strategic approach to the management of rheumatoid arthritis with disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis 2010;69:987-94.
3. Smolen JS, Aletaha D, Bijlsma JW, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis 2010;69:631-7.
4. Smolen JS, Landewe R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis 2010;69:964-75.
5. Rantalaiho V, Korpela M, Laasonen L, et al. Early combination disease-modifying antirheumatic drug therapy and tight disease control improve long-term radiologic outcome in patients with early rheumatoid arthritis: the 11-year results of the Finnish Rheumatoid Arthritis Combination Therapy trial. Arthritis Res Ther 2010;12:R122.
6. Landewe RB, Boers M, Verhoeven AC, et al. COBRA combination therapy in patients with early rheumatoid arthritis: long-term structural benefits of a brief intervention. Arthritis Rheum 2002;46:347-56.
7. Schipper LG, van Hulst LT, Grol R, et al. Meta-analysis of tight control strategies in rheumatoid arthritis: protocolized treatment has additional value with respect to the clinical outcome. Rheumatology (Oxford) 2010;49:2154-64.
8. Bakker MF, Jacobs JW, Verstappen SM, et al. Tight control in the treatment of rheumatoid arthritis: efficacy and feasibility. Ann Rheum Dis 2007;66 Suppl 3:iii56-60.
9. Mease PJ. Improving the routine management of rheumatoid arthritis: the value of tight control. J Rheumatol 2010;37:1570-8.
10. Boers M, Verhoeven AC, Markusse HM, et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet 1997;350:309-18.
11. Grigor C, Capell H, Stirling A, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. Lancet 2004;364:263-9.
12. Schipper LG, van Riel PL. Ups and downs in the treatment strategies of rheumatoid arthritis: Is it better to use the step-up or step-down approach in treatment? Rheumatology (Oxford) 2010;doi:10.1093/rheumatology/keq235.
13. Braun J, Rau R. An update on methotrexate. Curr Opin Rheumatol 2009;21:216-23.
14. Visser K, van der Heijde D. Optimal dosage and route of administration of methotrexate in rheumatoid arthritis: a systematic review of the literature. Ann Rheum Dis 2008;68:1094-9.
15. 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.
16. Salliot C, van der Heijde D. Long-term safety of methotrexate monotherapy in patients with rheumatoid arthritis: a systematic literature research. Ann Rheum Dis 2009;68:1100-4.
17. Verstappen SM, Jacobs JW, van der Veen MJ, et al. Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open label trial). Ann Rheum Dis 2007;66:1443-9.
18. van Everdingen AA, Jacobs JW, Siewertsz van Reesema DR, et al. Low-dose prednisone therapy for patients with early active rheumatoid arthritis: clinical efficacy, disease-modifying properties, and side effects: a randomized, double-blind, placebo-controlled clinical trial. Ann Intern Med 2002;136:1-12.
19. Kirwan JR, Bijlsma JW, Boers M, et al. Effects of glucocorticoids on radiological progression in rheumatoid arthritis. Cochrane.Database.Syst.Rev. 2007:CD006356.

20. Haugeberg G, Strand A, Kvien TK, et al. Reduced loss of hand bone density with prednisolone in early rheumatoid arthritis: results from a randomized placebo-controlled trial. Arch Intern Med 2005;165:1293-7.
21. Scott DL, Pugner K, Kaarela K, et al. The links between joint damage and disability in rheumatoid arthritis. Rheumatology (Oxford) 2000;39:122-32.
22. 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.
23. Prevoo ML, van 't Hof MA, Kuper HH, et al. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38:44-8.
24. Bijlsma JWJ, Oude Heuvel CH, Zaalberg A. Development and validation of the Dutch questionnaire capacities of daily life (VDF) for patients with rheumatoid arthritis. J Rehabil Sci 1990;3:71-4.
25. van der Heijde DM, van Riel PL, Nuver-Zwart IH, et al. Effects of hydroxychloroquine and sulphasalazine on progression of joint damage in rheumatoid arthritis. Lancet 1989;1:1036-8.
26. Schett G, Saag KG, Bijlsma JW. From bone biology to clinical outcome: state of the art and future perspectives. Ann Rheum Dis 2010;69:1415-9.
27. Michaud K, Messer J, Choi HK, et al. Direct medical costs and their predictors in patients with rheumatoid arthritis: a three-year study of 7,527 patients. Arthritis Rheum 2003;48:2750-62.
28. Fuchs VR. How to think about future health care spending. N Engl J Med 2010;362:965-7.
29. Schoels M, Wong J, Scott DL, et al. Economic aspects of treatment options in rheumatoid arthritis: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis 2010;69:995-1003.
30. Graudal N, Jurgens G. Similar effects of disease modifying anti rheumatic drugs, glucocorticoids and biologics on radiographic progression in rheumatoid arthritis: meta-analysis of 70 randomised placebo or drug controlled studies including 112 comparisons. Arthritis Rheum 2010;62:2852-63.
31. Hoes JN, Jacobs JW, Verstappen SM, et al. Adverse events of low- to medium-dose oral glucocorticoids in inflammatory diseases: a meta-analysis. Ann Rheum Dis 2009;68:1833-8.
32. van Everdingen AA, Siewertsz van Reesema DR, Jacobs JW, et al. The clinical effect of glucocorticoids in patients with rheumatoid arthritis may be masked by decreased use of additional therapies. Arthritis Rheum 2004;51:233-8.

Chapter 7

# The individual dose response relation for MTX: factors associated with the optimally effective MTX dose in individual patients with early rheumatoid arthritis

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## ABSTRACT

### Objective

The methotrexate (MTX) dose is often stepwise increased in active RA. However, optimal dose is probably different among patients. We determined the optimal MTX dose in individual patients and explored whether this dose and the level of disease activity at that dose can be predicted.

### Methods

Within the tight control and conventional MTX-based strategies in early RA of the CAMERA trial, for each patient curves were fitted for disease activity over time, to find the MTX dose after which further step-up did not result in clinically relevant improvement anymore (decrease >0.15 DAS28 units per month): the 'lowest optimally effective MTX dose (LOED)'. Using regression techniques, the association of demographic and clinical characteristics at baseline with this LOED and with the level of disease activity reached was studied.

### Results

In 208/299 patients LOED could be determined, mostly 15 mg/wk, 20 mg/wk, and 25 mg/wk. The average highest MTX dose was higher than the average LOED, suggesting overtreatment. Higher baseline disease activity, body height and lower HAQ values were predictive of higher LOEDs. LOED was associated with the DAS28 reached. Predictive ability of models was insufficient to allow use in individual patients.

### Conclusion

Using MTX dosing strategies with a maximal dose of 30 mg/wk for all patients might result in overtreatment. A starting dose of 15 mg/wk might be a good choice for most patients. Systematically monitoring disease activity over time in a tight-control strategy allows to determine when to stop increasing the dose.

## INTRODUCTION

Disease activity should be controlled as soon as possible in early rheumatoid arthritis (RA) to prevent radiographic joint damage and (resulting) functional limitations.[1-3] Methotrexate (MTX) is the disease modifying anti-rheumatic drug (DMARD) of first choice in early RA.[1, 2, 4] The drug is used in several step-up and step-down treatment strategies and is often used in combination with biologicals.[2, 5, 6] According to recent guidelines the dose should be increased quickly, but there are no generally accepted dose steps.[1, 4] In clinical practice dosing of MTX varies between 7.5 mg/wk and 30 mg/wk and clinical intuition is that different patients might need different dosing for optimal disease control.

Prediction of response to MTX is generally not reliable enough to decide on the start of MTX in individual patients or to determine the optimal dose of MTX.[7-9] Therefore the MTX dose is usually stepwise increased from a low (insufficient) dose until optimal disease control or toxicity: a step-up strategy. Another strategy might be to start with a high(er) dose and decrease the dose when the disease is sufficiently controlled: a step-down strategy. The timing and specific 'rules' regarding dose adjustments of MTX vary in clinical practice but a tight control principle (with MTX) has been proven to be useful in the treatment of RA as also mentioned in recent guidelines.[1, 5] Tight control can be defined as a treatment strategy, aimed at a specific target of low disease activity or remission in which disease activity is regularly monitored and treatment is adjusted accordingly.[10-14] The steps regarding (dose) adjustment of treatment are often predefined, and tight control strategies including protocolized treatment adjustments are found to be more effective on the group level.[14] However, it could well be that for an individual patient after reaching a certain MTX dose, further dose increments do not result in further clinically relevant improvement. This could lead to overtreatment with MTX and a delay in taking further, more effective strategy steps (i.e. undertreatment). Also a specific fixed starting dose of MTX could be too low for certain patients, leading to undertreatment because of unnecessary delay in optimal disease control.

Therefore, it would be of value to know the lowest dose of MTX which is optimally effective in lowering disease activity in individuals (i.e. the dose at which a further dose step will not clinically relevantly improve disease activity anymore). This 'lowest optimally effective dose' (LOED) could then serve as a starting dose or a dose to reach as soon as possible and/or as a dose after which other treatment strategy steps (i.e. combining or switching therapy) have to be considered if disease activity is still too high. Furthermore, the level of disease activity that can be reached with LOED would also be valuable to know. If sufficient disease control is not to be expected with MTX monotherapy, a combination (DMARD) treatment with MTX might be considered (using a step-down strategy) from the start of treatment.

The systematic up titration of the dose of MTX monotherapy from 7.5 mg/wk until 30 mg/wk in the Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA) trial comprises an ideal opportunity to study the dose response relation of MTX in individual patients.

The aim of the current study was to determine (variation in) the LOED and to investigate whether LOED and the level of disease activity reached with this dose can be predicted.

## PATIENTS AND METHODS

The follow-up data of all patients from the CAMERA trial was used for the time they were on oral MTX mono-therapy, i.e. the time until they started the next strategy step, or dropped out of the study.[15] Within the CAMERA trial a tight control (TC) MTX-based strategy was compared to a conventional, usual care (CT) strategy with MTX in early DMARD-naïve RA patients. In both strategies oral MTX was up-titrated from 7.5 mg/wk until 30 mg/wk (or maximum tolerable dose) in steps of 5 mg/wk (first step 2.5 mg/wk) if disease activity showed <20% improvement since the previous monthly assessment and there was no remission in the TC strategy and in the CT strategy if the number of swollen joints had not decreased since the previous three-monthly assessment and there was no remission. If 30 mg/wk of MTX (or the maximum tolerable dose) was reached with insufficient clinical effect a next step in the strategy could be taken. It was found that the TC strategy was more effective in reducing the disease activity over 2 years.[16]
For the current analysis the disease activity score based on 28 joints (DAS28) was used as the measure of disease activity.[17] Further, data on age, gender, rheumatoid factor (RF) status, weight, length, kidney (creatinine) and liver function (ALAT and ASAT), and functional disability (Health Assessment Questionnaire, HAQ) was available.

### Determination of Lowest Optimally effective MTX Dose (LOED)

To estimate the course of the disease activity over time within each patient the DAS28 measurements over time were plotted per patient. To control for the (natural, random) variation in DAS28 and attain the (smooth) curve of disease activity over time within individual patients, a non-linear model (power curve) was fitted for the DAS28 measurements over time for each patient. For every patient at every visit the predicted DAS28 according to this model was determined and then the highest MTX dose (increase) which still resulted in a clinically relevant improvement in (predicted) DAS28, the LOED, was determined per patient. If a patient never improved clinically relevantly or if a patient was still improving on his last MTX dose (increase), LOED was undetermined. An improvement in DAS28 of 0.15 per month (i.e. a decrease significantly smaller than the minimal important difference in DAS28 over 3 months [18]) was defined as the threshold for clinical relevance. Figure 1 shows an illustrative example of one patient's dose response curve and how the LOED was determined in this specific patient.
The fit of the individual curves of DAS28 over time to the observed DAS28 values was investigated graphically by comparing predicted and observed DAS28 values and check for systematic differences between observed and predicted values.

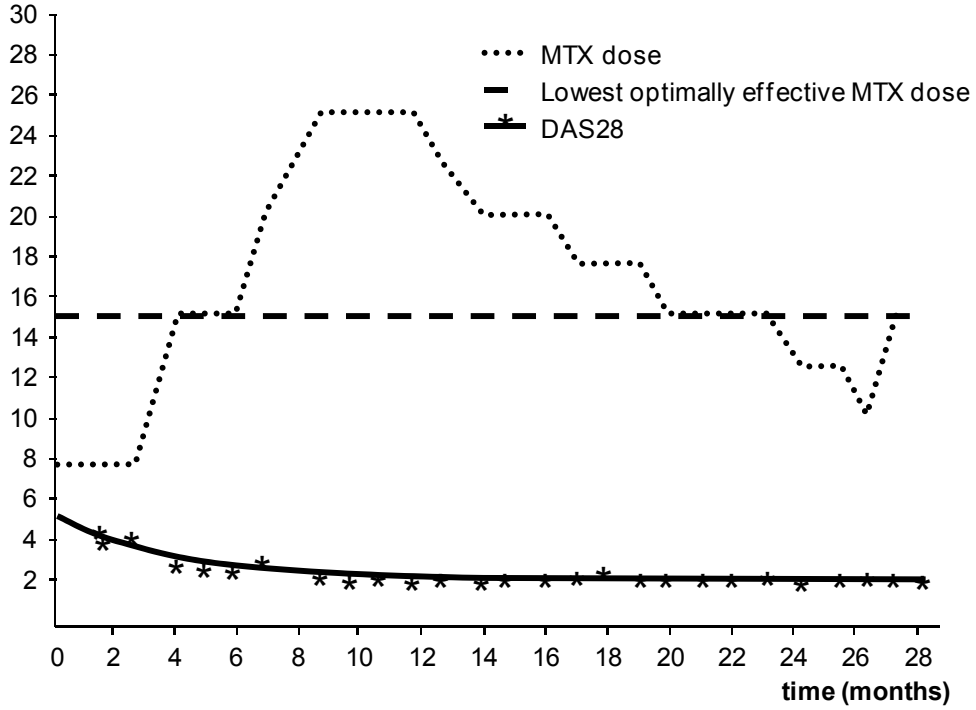


**Figure 1.** Example of determination of the dose response curve and lowest optimally effective MTX dose (LOED) in an individual patient.
The solid line represents the dose-response curve whereas the stars represent individual DAS28 measurements over time; dotted line represent MTX dose over time; dashed line represents the 'lowest optimally effective MTX dose' (LOED) as determined in this patient.

LOEDs were described and compared to the highest MTX dose reached to detect overtreatment. To detect possible undertreatment, the time until LOED was reached (i.e. time on suboptimal MTX dose) and the disease activity level reached were calculated. Analyses were performed both overall and by treatment strategy.

**Association of demographic and clinical variables with LOED and DAS28 reached**

Using multinomial logistic regression the association between demographic and clinical characteristics at baseline with LOED was studied, correcting for treatment strategy. The predictive properties of the model were investigated by calculating the predicting probabilities for the different LOEDs according to model and compare these probabilities to the observed probabilities (i.e. probabilities of different LOEDs as calculated in groups of patients defined by their predicted probabilities).

Using multivariate linear regression the effects of clinical and demographic characteristics at baseline and LOED on the level of disease activity reached at LOED were investigated, correcting for treatment strategy. Since this was a first attempt to look at a set of possible predictive factors univariate and multivariate regression analyses were performed using a manual blockwise backward selection strategy based on a liberal p-value for statistical significance ($p<0.2$) and explained variance (only for linear regression). A possible modifying effect of treatment strategy was also investigated in both regression analyses.

A sensitivity analysis was performed using different thresholds for clinical relevance of decrease in disease activity. The statistical package SAS 9.1 was used for all analyses.

## RESULTS

### Determination of LOED

Of 299 patients in the CAMERA trial, a sufficient number of DAS28 measurements on oral MTX were available to fit a curve over time and calculate predicted DAS28 scores for 290 patients (148 TC/142 CT). On graphically inspection, the predicted and observed DAS28 values in general showed a good fit of the model to the individual patient data, indicating that the model adjusted adequately for the natural variation in disease activity (Figure 2).

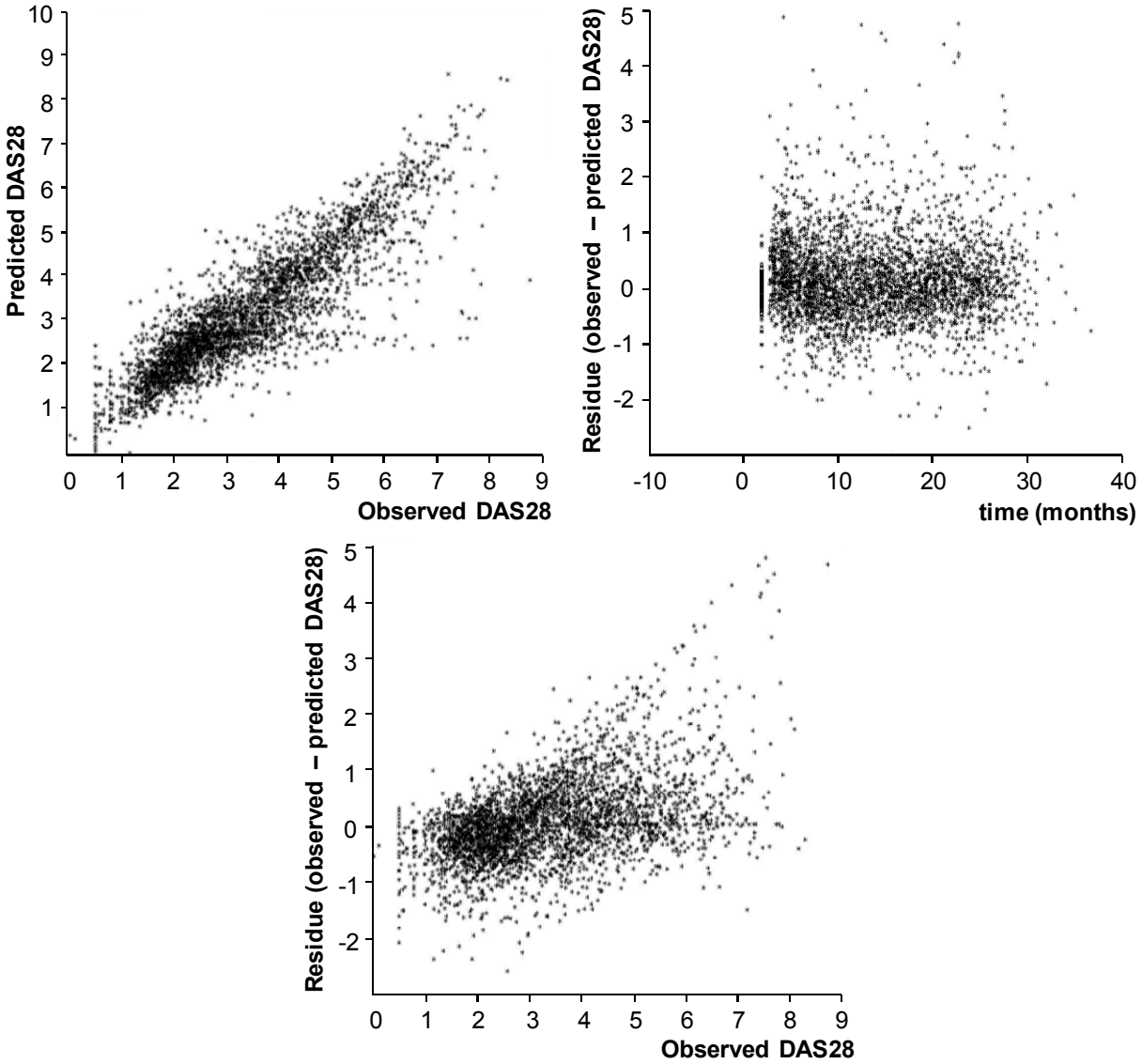


**Figure 2A-C.** Fit of individual curves to observed data.
A: The observed DAS28 score (x-axis) is related to the predicted DAS28 score (y-axis).
B: The residue (observed DAS28 minus predicted DAS28, y-axis) is shown over follow-up time, i.e. months (x-axis).
C: The residue (observed DAS28 minus predicted DAS28) (y-axis) is shown over observed DAS28 (x-axis).

Sixty-three patients (21 TC/42 CT) did not reach a (predicted) clinically relevant DAS28 decrease over time at all (i.e. non-responders) and 19 (11 TC/8 CT) patients still had a clinically relevant improvement on their last MTX dose. In the remaining 208 (116 TC/92 CT) patients LOED could be determined.

Table 1 shows the demographic and clinical baseline characteristics of the patients for whom LOED could be calculated, overall and by treatment group. No differences in clinical and demographic characteristics between the strategy groups were observed, but as expected due the specific treatment strategies the highest MTX dose given, the number of DAS28 measurements and the EULAR response at 3 months were higher in the TC strategy.

| **Characteristic** | **Total** n = 208 | **TC** n = 116 | **CT** n = 92 |
|---|---|---|---|
| Age (years) | 54 (14) | 55 (14) | 53 (15) |
| Female gender (%) | 142 (68) | 82 (71) | 60 (65) |
| RF positive (%) | 165 (87) | 92 (87) | 73 (88) |
| DAS28 baseline | 5.7 (1.1) | 5.7 (1.1) | 5.7 (1.0) |
| HAQ baseline | 1.2 (0.6) | 1.2 (0.6) | 1.3 (0.6) |
| Highest MTX dose (mg/wk) | 21.8 (6.9) | 25.1 (6.0) | 17.7 (5.6) |
| No. DAS28 measurements | 14.3 (7.5) | 19.3 (6.5) | 8.0 (2.2) |
| Maximum follow-up | 23.2 (6.7) | 22.8 (6.9) | 23.7 (6.3) |
| EULAR response (3 months) | | | |
| Good (%) | 46 (25) | 36 (34) | 10 (12) |
| Moderate (%) | 87 (47) | 49 (47) | 38 (47) |
| No (%) | 53 (28) | 20 (19) | 33 (41) |
| Length (cm) | 170.9 (9.0) | 170.6 (9.1) | 172.1 (9.0) |
| Weight (kg) | 73.8 (12.2) | 74.3 (13.6) | 73.0 (10.1) |
| BMI | 25.4 (3.8) | 25.3 (4.2) | 25.5 (3.4) |
| Serum creatinine (mmol/l) | 72.5 (14.1) | 73.3 (15.3) | 71.8 (12.8) |
| Creatinine clearance (ml/min) | 94.5 (24.8) | 92.5 (26.2) | 96.9 (23.2) |
| Optimal MTX dose (LOED) | 14.1 (7.2) | 17.7 (7.2) | 9.7 (4.1) |
| 5 mg/wk (%) | 2 (1) | 2 (1.5) | 0 (0) |
| 7.5 mg/wk (%) | 93 (44) | 24 (21) | 73 (76) |
| 10 mg/wk (%) | 1 (0.5) | 0 (0) | 1 (1) |
| 15 mg/wk (%) | 48 (23) | 32 (27.5) | 16 (17) |
| 20 mg/wk (%) | 30 (14.5) | 25 (21.5) | 5 (5) |
| 25 mg/wk (%) | 23 (11) | 22 (19) | 1 (1) |
| 30 mg/wk (%) | 11 (5) | 11 (9.5) | 0 (0) |
| Time at optimal MTX dose (months) | 4.1 (3.3) | 4.6 (2.7) | 3.5 (3.8) |
| Reached DAS28 at LOED | 3.7 (1.5) | 3.2 (1.3) | 4.4 (1.5) |

**Table 1** Demographic and clinical characteristics including early response and lowest optimally effective MTX dose (LOED) of patients in both strategy arms.

Values are mean (sd) for all continuous variables and number of patients (%) for all categorical variables.

TC= tight control strategy; CT= conventional strategy; RF= rheumatoid factor; DAS28= disease activity score based on 28 joints; HAQ= Health Assessment Questionnaire; MTX= methotrexate; BMI= body mass index; LOED= lowest optimally effective MTX dose.

The baseline clinical and demographic characteristics differed from the total CAMERA population in that they (as expected) had somewhat less non-responders and a somewhat higher follow-up time with more DAS28 measurements on oral MTX (data not shown).
For the whole group, the most common individual LOEDs were 7.5 mg/wk, 15 mg/wk, 20 mg/wk and 25 mg/wk MTX. In the CT group LOEDs were generally lower, 7.5 mg/wk was the most prevalent optimally effective dose in the CT group; this was 15 mg/wk in the TC group. On average (SD) the optimally effective dose was 14.1 (7.2), 17.7 (7.2) in TC and 9.7 (4.1) in CT.
When looking at the disease activity over time for the different LOED groups, in the 7.5 mg/wk group the disease activity was lower at baseline and decreased only slightly, mainly in the first months after baseline (Figure 3). This is also reflected in the finding that over 75% of patients in the 7.5 mg/wk groups were non-responders (EULAR good response) at three months and that about 95% of these patients did not clinically importantly further improve before 6 months (and thus have a low calculated LOED).

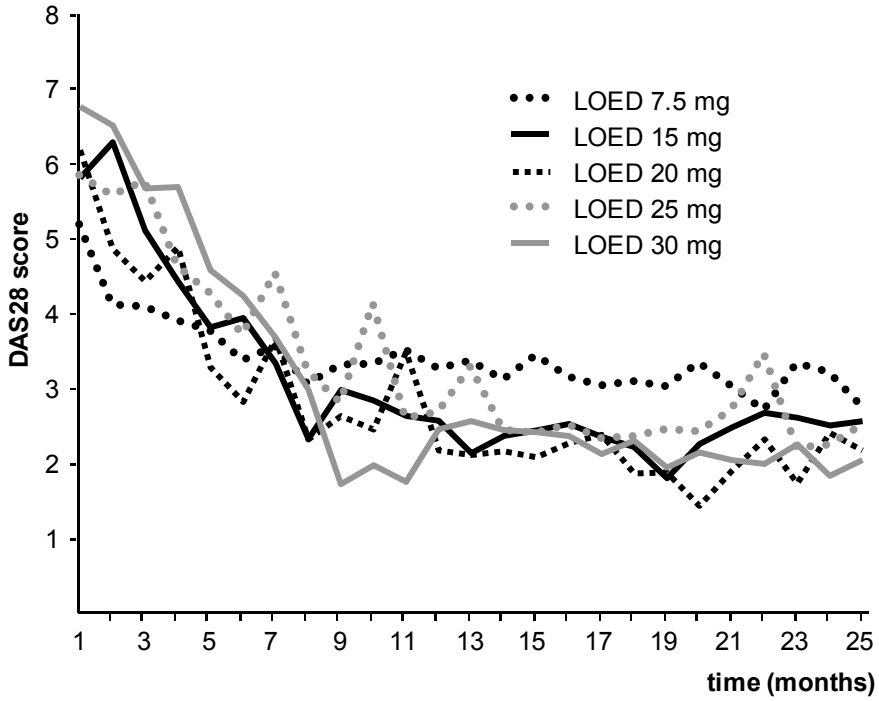


**Figure 3.** The disease activity course for groups of patients with different optimally effective MTX doses represented over time (i.e. in months).
The dotted black line represents 7.5 mg/wk; black line 15 mg/wk; blocked black line 20 mg/wk line; dotted grey line 25 mg/wk; solid grey line 30 mg/wk.

The average DAS28 that was reached with the optimal MTX dose was 3.2 (1.3) in the TC group and 4.4 (1.5) in the CT group.
The average highest MTX dose reached in individual patients was higher than the average LOED (Table 1) and about 31% of patients in both strategies were treated with a higher MTX dose then the calculated LOED, suggesting overtreatment. LOED was reached in about 4 months in both strategy groups.

**Association of demographic and clinical variables with LOED and DAS28 reached**

Table 2 shows the results of regression analysis with LOED as dependent variable. Only the most prevalent optimally effective dosages (i.e. combination of 7.5 mg/wk and non-response, 15 mg/wk, 20 mg/wk and 25 mg/wk) were taken into account in this analysis. The results show individual intercepts and estimates for the regression coefficients for the predictors per optimally effective MTX dose and the 7.5 mg/'non-response' category was used as reference (i.e. estimated odds ratio's refer to the odds of the respective LOED as compared to the odds of 7.5 mg/'non-response' being the LOED).

| Variable | LOED | Estimate | OR | 95%CI | p |
|---|---|---|---|---|---|
| Tight control strategy | 15 mg | 1.57 | 4.82 | 1.77 - 13.10 | <0.0001 |
| Tight control strategy | 20 mg | 2.35 | 10.53 | 2.74 - 40.50 | |
| Tight control strategy | 25 mg | 3.72 | 41.51 | 5.08 - 339.01 | |
| DAS28 baseline | 15 mg | 0.50 | 1.64 | 0.94 - 2.87 | 0.013 |
| DAS28 baseline | 20 mg | 1.04 | 2.83 | 1.47 - 5.46 | |
| DAS28 baseline | 25 mg | 0.63 | 1.89 | 0.94 - 3.79 | |
| HAQ baseline | 15 mg | -0,67 | 0.51 | 0.22 - 1.19 | 0.195 |
| HAQ baseline | 20 mg | -0.41 | 0.66 | 0.24 - 1.80 | |
| HAQ baseline | 25 mg | 0.45 | 1.57 | 0.56 - 4.39 | |
| Length (cm) | 15 mg | -0.01 | 0.99 | 0.93 - 1.05 | 0.030 |
| Length (cm) | 20 mg | 0.09 | 1.10 | 1.00 - 1.17 | |
| Length (cm) | 25 mg | 0.02 | 1.02 | 0.95 - 1.09 | |

**Table 2** Results of the multinomial regression analysis with lowest optimally effective MTX dose (LOED) as dependent variable.

The results show individual intercepts and estimates for the regression coefficients for the predictors per optimally effective MTX dose (LOED) and the 7.5 mg/'non-response' category was used as reference (i.e. estimated odds ratio's refer to the odds of the respective LOED as compared to the odds of 7.5 mg/'non-response' being the LOED). LOED= lowest optimally effective MTX dose; OR= odds ratio; CI= confidence interval; DAS28= disease activity score based on 28 joints; HAQ= Health Assessment Questionnaire.

A higher DAS28 and body height of the patient at baseline were statistically significantly associated with a higher optimally-effective MTX dose (as compared to 7.5 mg/'non-response'). A higher HAQ indicating more physical disability was associated with a lower chance of 15 mg/wk and 20 mg/wk as LOED but a higher chance of 25 mg/wk and HAQ (not statistically significant at 0.05 level). Treatment strategy did not modify the effect of the predictors, but the TC strategy was positively associated with higher LOEDs.

According to the model the probability of LOED being 15 mg/wk varied from 2% to 43%, 20 mg/wk from 1% to 70% and 25 mg/wk from 1% to 51%. Table 3 shows the observed probability of LOED being 15 mg/wk, 20 mg/wk or 25 mg/wk in groups defined according to the quartiles of the predicted probability. The calibration of the model seems reasonable, but probabilities are not high.

| Quartile | LOED 15 mg/wk | LOED 20 mg/wk | LOED 25 mg/wk |
|---|---|---|---|
| 1st | 8.1% | 0% | 0% |
| 2nd | 10.3% | 5.2% | 2.7% |
| 3rd | 27.0% | 7.9% | 21.1% |
| 4th | 18.4% | 34.2% | 24.3% |

**Table 3** Observed probabilities for lowest optimally effective MTX dose LOED of 15, 20 and 25 mg/wk in groups of patients defined according to the quartiles of the predicted probability.
Quartiles are based on the predicted probability according to the regression model (1st Quartile= 25% of patients with the lowest predicted probability; 4th Quartile= 25% of patients with the highest predicted probability). Percentages show the observed frequency of the specific LOED with increasing predicted probability (i.e. quartile) for the specific LOED (i.e.15 mg/wk, 20 mg/wk and 25 mg/wk for the different columns).

Table 4 shows the results of the linear regression analysis with DAS28 reached at LOED as dependent variable. Female gender, a higher HAQ and BMI were all associated with a higher DAS28 reached. The model explained 26% of the variance.

| Variable | Estimate | 95%CI | p |
|---|---|---|---|
| Intercept | 1.40 | -0.44 - 3.24 | 0.139 |
| Tight control strategy | -0.95 | -1.40 - -0.50 | <0.001 |
| Female gender | 0.83 | 0.34 - 1.32 | 0.001 |
| HAQ baseline | 0.23 | -0.11 - 0.57 | 0.193 |
| BMI | 0.08 | 0.01 - 0.15 | 0.030 |

**Table 4** Results of linear regression analysis with DAS28 value reached as dependent variable.
Higher values of HAQ imply more functional disability. CI= confidence interval; HAQ= Health Assessment Questionnaire; BMI= body mass index.

Adding EULAR good response at three months to this model increased the explained variance to 31%, but HAQ was no longer associated (at a significance level of 0.20) with the DAS28 reached (data not shown). Treatment strategy did not modify the effect of the predictors, but as expected, the TC strategy was related to lower disease activity.
In a separate analysis a higher LOED was also found to be related to a lower level of disease activity reached with 20 mg/wk comprising the best results.
When the definition for a clinically relevant improvement in disease activity was set at 0.05 DAS28 points per month the number of patients for which a LOED could be defined was lower, more patients were still improving (i.e. 59 instead of 19) and less patients never improved (41 instead of 63). The frequency of the LOEDs changed marginally with a lower frequency of 7.5 mg/wk as LOED (37% instead of 45%). Importantly, the factors associated with LOED and DAS28 were the same (data not shown). With other definitions the number of patients for which LOED could be determined varied but the distribution of the LOEDs were similar.

## DISCUSSION

Different LOEDs can be determined in individual RA patients using data on improvement in disease activity over time in relation to increases in MTX dose. This LOED might be predicted by baseline disease activity, the length of a patient and possibly the functional disability.

The current set of predictive factors does not provide enough certainty on the LOED for an individual patient, but it was found that a MTX dose of 15 mg/wk was the lowest dose that was classified as optimal. Although 7.5 mg/wk was found more often, this dose can probably not be regarded an optimally effective dose because the initial improvement is probably due to regression to the mean.

This knowledge might facilitate a more optimal and individualized MTX treatment strategy using 15 mg/wk as a starting dose for MTX in early RA and possibly even higher in patients with a high baseline DAS28 and length. This is in line with recent guidelines for MTX treatment.[1, 4-6, 19] If it is expected that disease activity will not improve sufficiently on MTX as single DMARD, starting (intensive) combination therapy could be considered (as soon as possible). To determine if a patient is expected to reach a satisfactory level of disease activity, information on the predictors for disease activity level reached and (especially) the course of disease activity over time should be considered; when the disease activity does not improve significantly anymore with an increase in MTX dose, other treatment options should be considered.

Using a standard dosing scheme for MTX as for instance in the CAMERA trial resulted in overtreatment in some patients (i.e. in 31% of patients the highest MTX dose was higher than LOED). LOED was reached in about 4 months and the average period that patients used oral MTX monotherapy was 23.2 (6.7) months. Taking into account that the average DAS28 was about 3.5, these findings suggest that a subgroup of the patients would have benefited from earlier adding or switching of treatment.

Interestingly, in the TC strategy of the CAMERA trial higher (optimal) MTX dosages were found, probably directly related to the strategy. First, a more frequent measurement of disease activity (as in the TC strategy) makes a more accurate estimation of the course of the disease activity over time possible. Second, the strict criteria for dose increase of MTX in the TC strategy mean that a lack of sufficient improvement in disease activity can not be explained by not increasing MTX dose. Therefore we believe that the doses as found in the tight control arm are closer to the ‘real’ optimal doses.

Our study has some limitations. First, results are based on the CAMERA trial in which the MTX dose was increased gradually from 7.5 mg/wk; nowadays in clinical practice patients are usually started on a higher dose.[2] This probably influences the course of the disease activity over time and the time of different dosing steps somewhat, but we do not expect this to influence LOED much. However, if MTX is started later in the disease course results might be different; similarly it is not clear whether LOED is constant over time in an individual. If for instance after a certain time on a stable MTX dose (i.e. LOED) disease

activity increases, would then an increase of the dose of MTX be effective? Further, this study is performed in patients for the period they used only MTX; results might be somewhat different if MTX is used together with other DMARDs, such as glucocorticoids.[20] Finally, higher doses of MTX might be used subcutaneously instead of orally (for toxicity reasons).[1, 2]

Although factors associated with LOED and DAS28 reached were found, the predictive value of the models was low as shown from the explained variances and absolute probabilities for the LOEDs. So the predictive value is probably not sufficient for treatment decisions in individual patients. Since the predictive value was determined in the same cohort as in which the model was developed in other cohorts the predictive value of the model will probably be lower. Further, the absolute probability for a certain optimal MTX dose is also depending on the specific definition of a 'clinically relevant improvement'. However, the predictors as found in this study are consistently related to a higher or lower LOED, suggesting that they are indeed important.

Part of the disease course in patients in which 7.5 mg/wk MTX was found as LOED might represent a structural small improvement over time misclassified as no improvement based on the cut-off regarding clinical relevance.

Because of the above limitations, the estimates of LOED should be repeated and the prediction models should be validated and extended (possibly with data used to monitor patients on MTX over time) in other cohorts with different treatment strategies.

In conclusion, a starting dose of MTX of at least 15 mg/wk seems a good initial choice based on our results. In patients with a higher disease activity and/or a higher body height, a higher starting MTX dose might be needed. However, if clinically toxicity is expected a lower dose might be started and the dose might be increased as soon as possible if tolerated. Combination (DMARD) treatment might be considered from start of treatment or early in the disease course if optimal disease control is not expected with MTX alone, especially in women with a high BMI and high disease activity.

To optimally monitor the effect of treatment, disease activity should be measured regularly (i.e. monthly) and the MTX dose, unless the treatment target is reached (TC), should be increased until no further improvement in disease activity is expected based on the curve of disease activity over time. In this case another strategy step (i.e. addition of a DMARD to the MTX or DMARD change) should be considered.

## REFERENCES


1. Combe B, Landewe R, Lukas C, et al. EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2007;66:34-45.
2. Smolen JS, Landewe R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis 2010;69:964-75.
3. Boers M. Understanding the window of opportunity concept in early rheumatoid arthritis. Arthritis Rheum 2003;48:1771-4.
4. 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.
5. Nam JL, Winthrop KL, van Vollenhoven RF, et al. Current evidence for the management of rheumatoid arthritis with biological disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of RA. Ann Rheum Dis 2010;69:976-86.
6. Gaujoux-Viala C, Smolen JS, Landewe R, et al. Current evidence for the management of rheumatoid arthritis with synthetic disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis 2010;69:1004-9.
7. Hider SL, Silman AJ, Thomson W, et al. Can clinical factors at presentation be used to predict outcome of treatment with methotrexate in patients with early inflammatory polyarthritis? Ann Rheum Dis 2009;68:57-62.
8. Wessels JA, van der Kooij SM, le Cessie S, et al. A clinical pharmacogenetic model to predict the efficacy of methotrexate monotherapy in recent-onset rheumatoid arthritis. Arthritis Rheum 2007;56:1765-75.
9. Maradit-Kremers H, Nicola PJ, Crowson CS, et al. Patient, disease, and therapy-related factors that influence discontinuation of disease-modifying antirheumatic drugs: a population-based incidence cohort of patients with rheumatoid arthritis. J Rheumatol 2006;33:248-55.
10. Bijlsma JW, Weinblatt ME. Optimal use of methotrexate: the advantages of tight control. Ann Rheum Dis 2007;66:1409-10.
11. Smolen JS, Aletaha D, Bijlsma JW, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis 2010;69:631-7.
12. Rantalaiho V, Korpela M, Laasonen L, et al. Early combination disease-modifying antirheumatic drug therapy and tight disease control improve long-term radiologic outcome in patients with early rheumatoid arthritis: the 11-year results of the Finnish Rheumatoid Arthritis Combination Therapy trial. Arthritis Res Ther 2010;12:R122.
13. Bakker MF, Jacobs JW, Verstappen SM, et al. Tight control in the treatment of rheumatoid arthritis: efficacy and feasibility. Ann Rheum Dis 2007;66 Suppl 3:iii56-60.
14. Schipper LG, van Hulst LT, Grol R, et al. Meta-analysis of tight control strategies in rheumatoid arthritis: protocolized treatment has additional value with respect to the clinical outcome. Rheumatology (Oxford) 2010;49:2154-64.
15. Bakker MF, Jacobs JWG, Welsing PMJ, et al. Are switches from oral to subcutaneous MTX or addition of cyclosporine to MTX useful steps in a tight control treatment strategy for RA? A post-hoc analysis of the CAMERA study. Ann Rheum Dis 2010;69:1849-52.
16. Verstappen SM, Jacobs JW, van der Veen MJ, et al. Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open label trial). Ann Rheum Dis 2007;66:1443-9.
17. Prevoo ML, van 't Hof MA, Kuper HH, et al. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38:44-8.
18. van Gestel AM, Prevoo ML, van 't Hof MA, et al. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary

American College of Rheumatology and the World Health Organization/International League Against Rheumatism Criteria. Arthritis Rheum 1996;39:34-40.

19. Knevel R, Schoels M, Huizinga TW, et al. Current evidence for a strategic approach to the management of rheumatoid arthritis with disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis 2010;69:987-94.
20. Gorter SL, Bijlsma JW, Cutolo M, et al. Current evidence for the management of rheumatoid arthritis with glucocorticoids: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis 2010;69:1010-4.

Chapter 8

# Look beyond the DAS28: DAS28 is influenced by coexistence of tender points in patients with rheumatoid arthritis

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## ABSTRACT

### Objective

To explore the influence of tender points (TP) in patients with rheumatoid arthritis (RA) on the disease activity index DAS28, the disease activity score of 28 joints.

### Methods

200 consecutive patients with RA attending the outpatient clinic were assessed for tender and swollen joint counts (TJC and SJC respectively), visual analogue scales (VAS) for patient's general health (GH) and for pain, tender point count (TPC) according to the ACR-criteria for fibromyalgia (FM) and erythrocyte sedimentation rate (ESR). DAS28 was calculated for each patient. Patients were categorised according to four TPC classes: 0, 1-5, 6-10 and ≥11 tender points (TP). The influence of TPC classes on DAS28 and its individual components and VAS pain was explored and tested for significance by Kruskal-Wallis tests. Spearman correlations coefficients between TP and DAS28 and its components were calculated.

### Results

196 patients were eligible for evaluation: 70% was female, mean age was 59 years, median disease duration was 3.9 years, 65% had rheumatoid factor and median DAS28 was 3.1. 49% had active disease, defined as DAS28 >3.2. In 15% of patients, the TPC was ≥11, in 12% 6-10, in 30% 1-5 and in 43% 0. TPC significantly influenced DAS28 and its less objective components TJC and VAS-GH, but not the more objective components SJC and ESR. Similarly, TPC was strongly correlated with DAS28, TJC and VAS-GH, but not with SJC and ESR.

### Conclusion

DAS28 is influenced by coexistence of TP, even in the non-FM range, due to the strong association of TP with the less objective DAS28 components VAS-GH and TJC. When applying DAS28-guided individual treatment strategies, a full clinical evaluation of the patient is still required not to overlook factors, such as non-inflammatory generalized pain and TP, influencing the score and the therapeutic approach.

## INTRODUCTION

In rheumatoid arthritis (RA), treatment strategies tailored to the individual RA patient to achieve a predefined level of low disease activity or remission are nowadays advocated.[1, 2] For this aim, generally the 28 joint disease activity score (DAS28) is used.[3] However, DAS28 has been developed to evaluate disease activity status in groups of patients with RA participating in clinical trials, but has not been validated for use in the individual patient and the reliability of DAS28 for assessing disease activity in individual patients can be and is questioned.[4-6] Misclassification in low disease activity might be due to the fact that ankles and feet are not included in the DAS28.[6] Furthermore, in two recent studies DAS28 was reported to overestimate disease activity in patients with RA who also had fibromyalgia (FM);[7, 8] FM is reported to be co-existent in 12-17% of patients with RA.[9-11] In daily clinical practice, discrepancy between DAS28 and physician's impression of disease activity in RA patients especially seems to apply to those with tender points (TP), even if not fulfilling the ACR-criteria for FM. The aim of this study was to explore the influence of coexistence of TP in patients with RA on the DAS28.

## PATIENTS AND METHODS

In this explorative study, 200 consecutive outpatients with RA seen in one university hospital and four general hospitals, collaborating in the Utrecht Rheumatoid Arthritis Cohort study group, were included. All patients had established RA according to the 1987 American College of Rheumatology (ACR) criteria [12] and received anti-rheumatic medication according to treatment protocols used in all participating hospitals. All patients had given informed consent for evaluation of clinical data, related to these treatment protocols. During an outpatient clinic visit, erythrocyte sedimentation rate (ESR), 28 tender joint count (TJC), and 28 swollen joint count (SJC), visual analogue scale (VAS) for pain (0-100 mm; 100=worst score) and VAS general health (VAS-GH) (0-100; 100=worst score), were assessed and subsequently the DAS28 was calculated. In addition, the tender point count (TPC) according to the ACR criteria for FM was assessed.[13]

### Statistical analyses

Descriptive statistics were used to summarize the patient characteristics. Because of non-normal distribution of these data, median values are given with $10^{th}$-$90^{th}$ percentile values. Patients were categorised into four TPC classes: 0 TP, 1-5 TP, 6-10 TP and ≥11 TP. DAS28 and its individual components and VAS pain were explored in the different TP classes and tested for significance with Kruskal-Wallis tests. Spearman correlation coefficients were calculated between TPC and DAS28 and its individual components and VAS pain. A p-value $<0.05$ was considered statistically significant. Statistical analyses were carried out using SPSS version 16.0 and NCSS 2007.

## RESULTS

Of the 200 patients included, 4 were excluded from analyses because of missing data, leaving 196 eligible for evaluation. Patient characteristics are summarised in Table 1. According to published criteria on DAS28, 49% of the patients had active disease (8% with high (DAS28 ≥5.1) and 41% moderate disease activity (DAS28 3.2-5.1)); 14% had low disease activity (DAS28 2.6-3.2) and 37% remission (DAS28 <2.6).[3] Of all patients, 43% had no TP, 30% had a TPC of 1-5, 12% (15% of women versus 3% of men) had TPC of 6-10 and 15% (17% of women versus 8% of men) had a TPC ≥11, see Table 1. Overall, women had significantly more TP than men: median 2 versus 0, respectively ($p<0.005$).
Figure 1 shows that with increasing TPC, also median DAS28, TJC, VAS-GH and VAS pain increased, in contrast to ESR and SJC; ESR and SJC were not statistically significantly different between the 4 groups (Table 1). In accordance with these results, TPC correlated strongly with DAS28 (rho 0.35, $p<0.001$) and with TJC and VAS-GH (respectively rho 0.37 and 0.29, $p<0.001$) but not with SJC and ESR (respectively rho 0.008 and 0.14, $p>0.10$). VAS pain significantly correlated with TPC (rho 0.41, $p<0.001$) and DAS28 (rho 0.54, $p<0.001$).

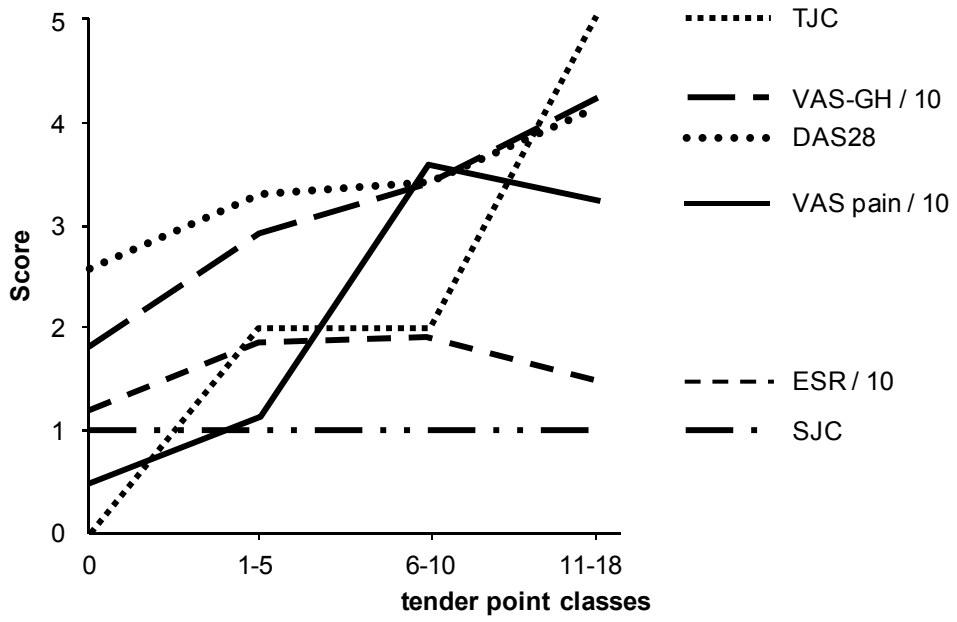


**Figure 1.** Median DAS28 and its individual components and VAS pain in the different tender point classes.
TPC 0, n=85; TPC1-5, n=59; TPC 6-11, n=23; TPC 11-18, n=29. DAS28= disease activity score assessing 28 joints; TPC= tender point count (0-18); TJC= tender joint count (0-28); SJC= swollen joint count (0-28); ESR= erythrocyte sedimentation rate (0-140 mm/1$^{st}$ hour), VAS-GH= visual analogue scale for general health (0-100; 100=worst score); VAS pain= visual analogue scale for pain (0-100; 100=worst score).

| Variable | Total<br>n = 196 | TPC 0<br>n = 85 (43%) | TPC 1-5<br>n = 59 (30%) | TPC 6-10<br>n = 23 (12%) | TPC ≥11<br>n = 29 (15%) | p |
|---|---|---|---|---|---|---|
| Age (years) | 59 (22-90) | 59 (37-77) | 56 (42-76) | 60 (43-79) | 61 (43-79) | ns |
| Gender (% female) | 70 | 58 | 73 | 91 | 83 | <0.005 |
| Disease duration (years) | 3.9 (0.6-8.9) | 4 (1-8) | 2 (1-8) | 5 (0-9) | 5 (1-8) | ns |
| RF positive (%) | 65 | 63 | 71 | 64 | 66 | ns |
| DAS28 | 3.1 (1.3-5.1) | 2.6 (1.2-4.8) | 3.5 (1.5-5.1) | 3.5 (1.9-5.2) | 4.1 (2.5-6.0) | <0.001 |
| TPC | 1 (0-13) | 0 | 2 (1-5) | 8 (6-10) | 16 (11-18) | na |
| TJC | 1 (0-9) | 1 (0-8) | 3 (0-10) | 6 (0-25) | 11 (0-22) | <0.001 |
| SJC | 1 (0-7) | 1 (0-8) | 2 (0-8) | 2 (0-12) | 2 (0-9) | ns |
| ESR (mm/1$^{st}$ hour) | 14 (3-41) | 12 (3-41) | 18 (4-49) | 19 (2-36) | 11 (0-22) | ns |
| VAS-GH (mm) | 26 (1-67) | 18 (0-30) | 15 (0-60) | 34 (9-79) | 42 (10-70) | 0.01 |
| VAS pain (mm) | 14 (0-66) | 6 (0-49) | 11 (0-69) | 36 (8-84) | 33 (3-79) | <0.001 |

**Table 1** Patient characteristics of total study population and its subgroups according to tender point classes.
All values are reported as median (10$^{th}$ to 90$^{th}$ percentile values), unless otherwise indicated.
RF= rheumatoid factor; DAS28= disease activity score; TPC= tender point count (0-18); TJC= tender joint count (0-28); SJC= swollen joint count (0-28); ESR= erythrocyte sedimentation rate (0-140 mm/1$^{st}$ hour); VAS-GH= visual analogue scale for general health (0-100 mm, 100 = worst score); VAS pain= visual analogue scale for pain (0-100 mm, 100 = worst); ns= not statistically significant; p<0.05= statistically significant; na= not applicable.

## DISCUSSION

DAS28 is a widely used instrument for assessing disease activity in patients with RA. Reliability of DAS28, representing disease activity in the individual patient can be questioned, especially if there is concomitant FM, as was shown in two recent studies,[7, 8] or if there are TP, as shown in our study. With increasing TPC, the less objective DAS28 components VAS general wellbeing and the TJC showed increasingly higher scores in contrast to the more objective DAS28 components ESR and SJC. This is in accordance with a previous study in which patients with FM but without RA showed high scores on the DAS28, but normal ESR values and no swollen joints.[14] This finding reduces the sensitivity of DAS28 to assess low disease activity or remission in individuals; other causes of a raised ESR than disease activity have the same effect. Absence of joints of feet in the DAS28 reduces the specificity applying the DAS28 for this aim.[6]

To improve the specificity of the DAS28 assessing remission in individuals in DAS28-guided individual tight control treatment strategies, one could add to the DAS28 criterion of remission the required criterion of absence of any for RA relevant swollen joint.

This study comprised a population based RA cohort visiting academic and general rheumatology outpatient clinics on a regular basis. In the Netherlands, virtually all patients with RA are treated by rheumatologists, not by general practitioners. Thus our sample reflects a common RA population. The prevalence of concomitant FM in our study population is not known. We choose to assess TP but not to apply the ACR criteria for FM, as the FM criterion chronic generalized pain is difficult to interpret in RA patients. Recently, the relevance of the ACR criteria for FM in clinical practice was questioned as these are classification criteria, so developed for classing groups especially for research; it has been suggested that in clinical practice, thus for individuals a TPC ≥6 might discriminate better patients with FM from those without FM.[15] In our study, this TPC also would interfere with the reliability of the DAS28.

In conclusion, the disease activity index DAS28 is influenced by coexistence of TP, even in the non-FM range, due to the strong association of TPC with the less objective DAS28 components VAS-GH and TJC. When applying DAS28-guided individual treatment strategies, a full clinical evaluation of the patient is still required not to overlook factors, such as non-inflammatory generalized pain and TP, influencing the score and the therapeutic approach.

## REFERENCES


1. Smolen JS, Landewe R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis 2010;69:964-75.
2. Bakker MF, Jacobs JW, Verstappen SM, et al. Tight control in the treatment of rheumatoid arthritis: efficacy and feasibility. Ann Rheum Dis 2007;66 Suppl 3:iii56-60.
3. Prevoo ML, van 't Hof MA, Kuper HH, et al. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38:44-8.
4. Taylor WJ, Harrison AA, Highton J, et al. Disease Activity Score 28-ESR bears a similar relationship to treatment decisions across different rheumatologists, but misclassification is too frequent to replace physician judgement. Rheumatology (Oxford) 2008;47:514-8.
5. Wolfe F, Michaud K, Pincus T, et al. The disease activity score is not suitable as the sole criterion for initiation and evaluation of anti-tumor necrosis factor therapy in the clinic: discordance between assessment measures and limitations in questionnaire use for regulatory purposes. Arthritis Rheum 2005;52:3873-9.
6. Landewe R, van der Heijde D, van der Linden S, et al. Twenty-eight-joint counts invalidate the DAS28 remission definition owing to the omission of the lower extremity joints: a comparison with the original DAS remission. Ann Rheum Dis 2006;65:637-41.
7. Coury F, Rossat A, Tebib A, et al. Rheumatoid arthritis and fibromyalgia: a frequent unrelated association complicating disease management. J Rheumatol 2009;36:58-62.
8. Ranzolin A, Brenol JC, Bredemeier M, et al. Association of concomitant fibromyalgia with worse disease activity score in 28 joints, health assessment questionnaire, and short form 36 scores in patients with rheumatoid arthritis. Arthritis Rheum 2009;61:794-800.
9. Naranjo A, Ojeda S, Francisco F, et al. Fibromyalgia in patients with rheumatoid arthritis is associated with higher scores of disability. Ann Rheum Dis 2002;61:660-1.
10. Wolfe F, Michaud K. Severe rheumatoid arthritis (RA), worse outcomes, comorbid illness, and sociodemographic disadvantage characterize RA patients with fibromyalgia. J Rheumatol 2004;31:695-700.
11. Wolfe F, Cathey MA, Kleinheksel SM. Fibrositis (Fibromyalgia) in rheumatoid arthritis. J Rheumatol 1984;11:814-8.
12. 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.
13. Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum 1990;33:160-72.
14. Leeb BF, Andel I, Sautner J, et al. The DAS28 in rheumatoid arthritis and fibromyalgia patients. Rheumatology (Oxford) 2004;43:1504-7.
15. Katz RS, Wolfe F, Michaud K. Fibromyalgia diagnosis: a comparison of clinical, survey, and American College of Rheumatology criteria. Arthritis Rheum 2006;54:169-76.

Chapter 9

# Misclassification of disease activity when assessing individual patients with early rheumatoid arthritis using disease activity indices which do not include joints of feet

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## ABSTRACT

### Objective

RA disease activity is often assessed in individual patients with DAS28 or other instruments, which exclude joints of feet. We evaluated whether this may lead to misclassification of disease activity in individuals.

### Methods

A cohort of RA patients was classed into 3 'regional radiographic damage progression' groups: those with predominantly progression in feet, those with similar progression in hands and feet, and those with predominantly progression in hands. This was done for progression early (0-2 years) and later (2-5 years) in the course of the disease. Baseline and mean DAS28, individual DAS28 variables, and tender (TJC) and swollen (SJC) joints counts of feet were compared between groups. The longitudinal relation of DAS28 with radiographic damage was investigated within the groups using a mixed model analysis with RF-status, baseline joint damage, and TJC and SJC of feet as covariates.

### Results

Early (n=265) and later (n=200) in the disease course, respectively, 55% and 33% had no radiographic progression, 11% and 16% predominantly foot, 23% and 35% similar, and 11% and 16% predominantly hand progression. Early RA predominantly foot progressors had a higher TJC 3.4 (2.2), and SJC 2.8 (1.9) of the feet compared to predominantly hand progressors: 1.5 (1.3) and 1.1 (1.2), both $p<0.001$, although DAS28 were similar. This difference was not present in the later course of the disease. In early RA, the longitudinal relation between DAS28 and radiographic progression was influenced by region of progression (predominantly foot progressors vs. others: $\beta=1.2$, 95%CI: 0.6-1.9, $p<0.001$), suggesting underestimation of disease activity when assessed by DAS28 in predominantly foot progressors. In this group, joint counts for feet were independently related to radiographic progression.

### Conclusions

During the first years of RA, DAS28 underestimates actual disease activity and the expected joint damage in the about 10% of patients with predominantly disease activity in feet.

## INTRODUCTION

The disease activity score based on 28 joints (DAS28) and other disease activity indices like the clinical disease activity index (CDAI) and simplified disease activity index (SDAI) are often used in clinical practice to assess disease activity in individual patients with rheumatoid arthritis (RA),[1, 2] although they are primarily designed for and mainly validated on the group level in clinical trials. In tight control strategies, these instruments, especially DAS28, are used to define treatment goals, also assuming a relation of the score with long-term outcome in individual patients.[3-5] However, these indices are based on 28 tender (TJC) and swollen (SJC) joint counts, excluding small joints of the feet. On the group level, these indices are highly correlated with more comprehensive joints counts and related to future joint damage,[6] but on the individual patient level, this relation is less clear.[7-9] The effectiveness of tight control strategies might be increased using a more personalized approach than those based on assessment of 28 joints only.[3, 10]
In patients with early RA radiographic joint damage starts earlier in feet (MTP5) than in hands [11] suggesting that joints of feet are important to asses in early RA, especially within the 'window of opportunity', when the need for optimal disease control is highest. Moreover, if specific groups of joints (i.e. those of feet or those of hands) are predominantly involved in individual patients, this might lead in those patients to under- or overestimation of disease activity with negative consequences in tight control treatment strategies when disease activity is assessed with (indices using) 28 joint counts only.
The aim of this investigation was to study whether groups of patients exist, especially early in the disease, with predominant involvement of the feet and whether this has consequences (when instruments excluding the joints of feet are used) for the estimation of 'real' disease activity and long-term radiographic outcome.

## PATIENTS AND METHODS

Patients who participated in a two-year randomised, open-label prospective multi-centre treatment strategy trial, the Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA),[12] were evaluated. Patients were included between 1999 and 2003. At study entry all patients fulfilled the 1987 revised American College of Rheumatology (ACR) criteria for RA,[13] had a disease duration of less than 1 year, and were disease modifying anti-rheumatic drug (DMARD) and glucocorticoid-naïve. Patients were randomized to either the tight control methotrexate (MTX) based treatment strategy or to the conventional MTX-based strategy; both strategies were aimed at remission.

### Radiographic progression

For radiographic damage, radiographs of hands and feet were evaluated according to the SharpvanderHeijde score (SHS) [14] by 2 readers, blinded to clinical information. Final SHS was based on consensus between the two observers. Yearly radiographs were available

and the mean yearly progression rate was calculated over a period from 0 to 5 years of follow-up and also separately early (from 0 to 2 years) and later (from 2 to 5 years) in the course of the disease. Total SHS and separate scores for hands and feet were calculated.

**Disease activity**

To assess disease activity, TJC and SJC based on 28 and 38 joints, respectively excluding and including feet, as well as a TJC and SJC for the feet only (10 joints), erythrocyte sedimentation rate (ESR) and visual analogue scales (VAS) for general well-being and pain were used. As disease activity index the DAS28 was computed from TJC and SJC of 28 joints, ESR, and VAS general well-being,[1] since DAS28 is generally used and EULAR response criteria are based on it.[1, 15]

**Classification according to regional radiographic joint progression**

To determine the specific joint involvement in individual patients, patients were classified into 3 'regional damage progression' groups: 1) predominantly progression of the feet (foot progressors), 2) similar progression of hands and feet (similar progressors), and 3) predominantly progression of the hands (hand progressors), and 4) those with no progression (non-progressors). These groups were determined based on the radiographic progression rates (mean SHS units increase per year) of both hands and feet. For all patients with SHS>0 the difference in radiographic progression of the feet (SHSfeet) and the hands (SHShands) was calculated. To calculate this 'difference score' (SHShands minus SHSfeet) the hands and feet scores were first normalized to a 0-100 scale because more hand than feet joints are included, so SHS for individual joints of hands and feet are different. Based on the distribution of this 'difference score', patients were classified as follows: patients in the first quartile (i.e. smallest (i.e. negative) difference of SHShands minus SHSfeet) were classified into the predominantly foot-progression group, patients in the last quartile (i.e. largest difference of SHShands minus SHSfeet) into the predominantly hand-progression group and all patients in between (25-75 quartile) were classified into the similar progression group. All patients with a SHS of 0 were classified as non-progressors.
This classification was performed over the total period and also separately for radiographic progression within the first 2 years and that between 2 and 5 years.

**Time-averaged clinical variables**

To summarize the clinical involvement of joints and disease activity in the different groups of patients, time-averaged values were calculated for the DAS28, its individual components (TJC, SJC, ESR, and VAS general well-being), and for TJC and SJC of the feet. For the period of 0-2 years, 3 monthly measurements were used for all variables. An average value was calculated if at least 7 out of 10 measurements were present, including the baseline value. For the period of 2-5 years only yearly measurements were available. An average value was calculated if at least 3 out of 4 measurements were available.

**Statistical analyses**

Baseline and time-averaged clinical variables (DAS28, its individual components, and TJC and SJC of feet) were compared between the 3 'regional damage progression' groups and the non-progression group within early and later in the course of RA.

To investigate whether the damage classification was stable over the 2 time periods (i.e. whether this could be considered a patient characteristic or a time varying characteristic of RA) a 4 by 4 table was constructed showing the percentages of patients staying in the same category or changing from category.

The longitudinal relation of DAS28 with radiographic damage over the 5 year period was investigated within all patients using longitudinal regression analysis (mixed model analysis), using an unstructured correlation structure with a random intercept and a linear link function. In this analysis the relation between DAS28 at time point 'x' was related to radiographic damage at time point 'x' + one year. This time interval was introduced since it takes time before damage resulting from (a period of) disease activity can be seen as joint damage on radiographs.[6, 16] It is also in line with the rationale of using DAS28 in making treatment decisions in individual patients, directed at the prevention of future damage. In this model rheumatoid factor (RF) status and baseline joint damage were used as covariates. The regression coefficient for the time varying independent variables in this model can be interpreted in terms of a cross-sectional relationship (for example patients with a high DAS28 have, on average, also a high damage score), as well as a longitudinal relationship (i.e. an increase or decrease in DAS28 is related to an increase or decrease in progression of joint damage). In this study, there was a particular interest in the longitudinal relationship. Therefore a first-order autoregressive analysis was performed, in which the value for the outcome variable (SHS) was adjusted for the value for the outcome variable at the previous time point (SHS one year earlier). This analysis can be interpreted as modelling change (progression) scores calculated per time interval. The rationale of this autoregressive analysis is that the radiographic damage score is determined by radiographic damage score one time point earlier and also by changes in independent variables. Similar analyses of the longitudinal relation between disease activity and radiographic damage have been performed before.[6]

It was also investigated within this model whether specific regional joint involvement (i.e. 'regional damage progression' groups) had an influence on progression of joint damage and whether this classification influenced the longitudinal relation between disease activity and joint damage by including a variable 'predominantly foot progressors vs. others' and the interaction of this variable with the variable for DAS28.

In a separate analysis the SJC and TJC of the feet were entered as covariates in the initial model to investigate whether this improved prediction of radiographic damage in all patients and within 'regional damage progression' groups.

Statistical software SPSS 15.0 and SAS 9.1 were used for analyses. P values $<0.05$ were considered statistically significant.

## RESULTS

Clinical characteristics for patients with no progression, predominantly foot, similar, and predominantly hand progression are given in Table 1A for the early RA period (0 to 2 years) and in Table 1B for the later RA period (2 to 5 years). In the early and later course of the disease, respectively 30 (11%) and 33 (16%) patients had predominantly foot progression, 60 (23%) and 69 (35%) similar progression, 30 (11%) and 32 (16%) predominantly hand progression, and 145 (55%) and 66 (33%) showed no radiographic progression. So at least one out of ten patients had predominantly foot involvement in the first 5 years of the disease. Baseline characteristics showed that SHS at baseline was significantly lower in the non-progressors compared to the 3 'regional damage progression' groups, both at 0-2 years as well as 2-5 years, (all $p<0.02$). Predominantly foot- and hand progressors had higher time-averaged radiographic damage (defined by total SHS) compared to similar progressors, both at 0-2 years as well as 2-5 years, (all $p<0.02$, except for predominantly hand progressors vs. similar progressors for 2-5 years: $p=0.21$. RF was also significantly different between the RA groups; non-progressors and predominantly hand progressors were less RF-positive when compared to predominantly foot and similar progressors. Finally, in early RA the TJC and SJC of the feet were higher in the predominantly foot progressors compared to the predominantly hand progressors ($p=0.048$ and $p=0.008$, respectively) (Table 1). This difference was not present anymore later in the course of RA (2-5 years).
Regarding outcome over time, over the first two years the predominantly foot and hand progressors had a similar mean (SD) DAS28 of respectively 4.0 (1.0) and 3.9 (0.9). Compared to the predominantly hand progressors, the predominantly foot progressors had higher time-averaged TJC and SJC of the feet: 3.4 (2.2) vs. 1.5 (1.3), $p<0.001$ and 2.8 (1.9) vs. 1.1 (1.2), $p<0.001$, respectively (Table 1A). This difference was not observed in for the 2-5 year period (Table 1B). In both time periods, the similar progression group had lower or in between disease activity scores and involvement of the feet compared to patients with predominantly foot or hand progression.

| | Foot | Hand ≈ Foot | Hand | Non-progressors |
|---|---|---|---|---|
| Characteristic | n = 30 | n = 60 | n = 30 | n = 145 |
| | **n (%)** | **n (%)** | **n (%)** | **n (%)** |
| Female gender | 21 (70) | 32 (53) | 21 (70) | 104 (72) |
| RF positive | 23 (77) | 45 (75) | 19 (63) | 81 (56) |
| | **mean (SD)** | **mean (SD)** | **mean (SD)** | **mean (SD)** |
| *Baseline (0 years)* | | | | |
| Age (years) | 47 (13) | 52 (16) | 59 (14) | 52 (14) |
| DAS28 | 5.5 (1.0) | 5.4 (1.1) | 5.6 (1.2) | 5.6 (1.0) |
| TJC28 | 8.3 (4.0) | 8.6 (5.2) | 9.6 (4.1) | 10.1 (6.0) |
| SJC28 | 8.9 (3.9) | 9.1 (5.0) | 10.6 (4.5) | 11.0 (5.4) |
| TJCfeet | 5.8 (3.1) | 4.9 (3.2) | 3.5 (2.7) | 4.9 (3.4) |
| SJCfeet | 5.6 (3.2) | 4.2 (3.2) | 3.0 (3.2) | 4.2 (3.3) |
| ESR (mm/h$^{1st}$) | 45 (33) | 39 (27) | 44 (33) | 36 (22) |
| VAS general (mm) | 51 (23) | 52 (23) | 54 (24) | 54 (21) |
| VAS pain (mm) | 60 (27) | 50 (29) | 47 (26) | 51 (27) |
| *Time-averaged (0 - 2 years)* | | | | |
| DAS28 | 4.0 (1.0) | 3.2 (0.9) | 3.9 (0.9) | 3.3 (0.9) |
| TJC28 | 4.1 (2.6) | 3.0 (2.2) | 4.0 (2.0) | 3.3 (2.7) |
| SJC28 | 4.7 (3.0) | 3.1 (2.3) | 4.5 (2.7) | 3.1 (2.3) |
| TJCfeet | 3.4 (2.2) | 2.0 (1.8) | 1.5 (1.3) | 2.0 (1.8) |
| SJCfeet | 2.8 (1.9) | 1.2 (1.3) | 1.1 (1.2) | 1.2 (1.2) |
| ESR (mm/h$^{1st}$) | 31 (18) | 20 (12) | 27 (18) | 20 (12) |
| VAS general (mm) | 30 (18) | 23 (14) | 29 (18) | 27 (15) |
| | **median (IQR)** | **median (IQR)** | **median (IQR)** | **median (IQR)** |
| *Baseline (0 years)* | | | | |
| SHS total | 0.5 (0-6) | 0 (0-3) | 0 (0-9) | 0 (0-0) |
| *Time-averaged (0 - 2 years)* | | | | |
| SHS total | 6 (3-16) | 1 (0.5-2) | 4 (3-9) | 0 (0-0) |
| SHS hands | 0 (0-2) | 0.5 (0-1) | 4 (3-7) | 0 (0-0) |
| SHS feet | 5 (3-11) | 4 (2-6) | 0 (0-1) | 0 (0-0) |
| SHS hands-feet | -24 (-46- -16) | -3 (-8- -2) | 13 (10-31) | 0 (0-0) |

**Table 1A** Clinical, demographic, and time-averaged characteristics of the 3 'regional damage progression' groups and the non-progressors for early RA.

For all categorical variables number (%) of patients is shown. Mean (standard deviation, SD) is shown for all continuous variables, except for SHS where median (interquartile range, IQR) is shown. Foot= predominantly progression of foot; Hand ≈ Foot= similar progression of hand and foot; Hand= predominantly progression of hand; RF= rheumatoid factor; DAS28= disease activity score based on 28 joint count; TJC28= tender joint count, based on 28 joints; SJC28= swollen joint count, based on 28 joints; TJCfeet= tender joint count of the feet, based on 10 joints; SJCfeet= swollen joint count of the feet, based on 10 joints; ESR= erythrocyte sedimentation rate; VAS= visual analogue scale (0-100, latter is worst score); SHS= SharpvanderHeijde score, SHS hands-feet= normalized difference score of SHS feet minus SHS hands.

| | Foot | Hand ≈ Foot | Hand | Non-progressors |
|---|---|---|---|---|
| Characteristic | n = 33 | n = 69 | n = 32 | n = 66 |
| | **n (%)** | **n (%)** | **n (%)** | **n (%)** |
| Female gender | 27 (82) | 41 (59) | 19 (59) | 46 (70) |
| RF positive | 28 (85) | 54 (78) | 18 (56) | 30 (46) |
| | **mean (SD)** | **mean (SD)** | **mean (SD)** | **mean (SD)** |
| *Baseline (2 years)* | | | | |
| Age (years) | 54 (12) | 51 (13) | 55 (16) | 52 (15) |
| DAS28 | 5.3 (1.0) | 5.5 (1.1) | 5.8 (1.0) | 5.7 (1.2) |
| TJC28 | 7.6 (4.3) | 9.0 (5.5) | 9.9 (4.6) | 11.1 (6.2) |
| SJC28 | 9.3 (4.6) | 9.9 (4.8) | 11.1 (4.7) | 11.4 (5.6) |
| TJCfeet | 4.7 (3.0) | 4.7 (3.5) | 3.3 (3.2) | 5.1 (3.2) |
| SJCfeet | 4.1 (3.1) | 4.2 (3.4) | 2.8 (3.0) | 4.0 (3.3) |
| ESR (mm/h$^{1st}$) | 35 (22) | 40 (31) | 42 (26) | 36 (24) |
| VAS general (mm) | 53 (24) | 52 (22) | 51 (24) | 55 (20) |
| VAS pain (mm) | 48 (27) | 49 (30) | 50 (26) | 53 (26) |
| *Time-averaged (2 - 5 years)* | | | | |
| DAS28 | 2.6 (0.8) | 2.8 (1.0) | 2.9 (1.0) | 2.6 (1.0) |
| TJC28 | 1.5 (1.7) | 1.5 (1.7) | 1.8 (3.2) | 1.5 (2.4) |
| SJC28 | 1.5 (1.9) | 1.4 (1.9) | 1.8 (2.0) | 0.8 (1.4) |
| TJCfeet | 1.3 (1.7) | 1.1 (1.5) | 1.2 (1.9) | 1.1 (2.1) |
| SJCfeet | 0.5 (0.9) | 0.7 (1.1) | 0.3 (0.4) | 0.3 (0.7) |
| ESR (mm/h$^{1st}$) | 14 (10) | 18 (13) | 21 (14) | 17 (13) |
| VAS general (mm) | 20 (14) | 22 (18) | 19 (15) | 23 (14) |
| | **median (IQR)** | **median (IQR)** | **median (IQR)** | **median (IQR)** |
| *Baseline (2 years)* | | | | |
| SHS total | 0 (0-1) | 0 (0-1) | 0 (0-3) | 0 (0-0) |
| *Time-averaged (2 - 5 years)* | | | | |
| SHS total | 5 (4-8) | 1 (1-4) | 4 (2-9) | 0 (0-0) |
| SHS hands | 1 (0-3) | 1 (0-2) | 4 (2-7) | 0 (0-0) |
| SHS feet | 4 (3-5) | 1 (0-2) | 0 (0-1) | 0 (0-0) |
| SHS hands-feet | -21 (-36- -18) | -2 (-7-1) | 12 (6-21) | 0 (0-0) |

**Table 1B** Clinical, demographic, and time-averaged characteristics of the 3 'regional damage progression' groups and the non-progressors at 2-5 years.

For all categorical variables number (%) of patients is shown. Mean (standard deviation, SD) is shown for all continuous variables, except for SHS where median (interquartile range, IQR) is shown. Foot= predominantly progression of foot; Hand ≈ Foot= similar progression of hand and foot; Hand= predominantly progression of hand; RF= rheumatoid factor; DAS28= disease activity score based on 28 joint count; TJC28= tender joint count, based on 28 joints; SJC28= swollen joint count, based on 28 joints; TJCfeet= tender joint count of the feet, based on 10 joints; SJCfeet= swollen joint count of the feet, based on 10 joints; ESR= erythrocyte sedimentation rate; VAS= visual analogue scale (0-100, latter is worst score); SHS= SharpvanderHeijde score, SHS hands-feet= normalized difference score of SHS feet minus SHS hands.

Classification of the 'regional damage progression' groups was stable in 47% of all patients (i.e. the classification did not change over time between the 2 time periods). Of all patients with predominantly foot progression 48% stayed within this category in both RA periods; this

was 41% for similar progressors, 39% for predominantly hand progressors, and 51% for non-progressors (Table 2).

| | | Established RA (2 - 5 years) | | | |
|---|---|---|---|---|---|
| | | Foot | Hand ≈ Foot | Hand | Non-progressors |
| **Early RA (0 - 2 years)** | *n* | *33* | *67* | *31* | *66* |
| Foot | *23* | **11 (48)** | 10 (43) | 2 (9) | 0 (0) |
| Hand ≈ foot | *44* | 11 (25) | **18 (41)** | 7 (16) | 8 (18) |
| Hand | *23* | 3 (13) | 8 (35) | **9 (39)** | 3 (13) |
| Non-progressors | *107* | 8 (8) | 31 (29) | 13 (12) | **55 (51)** |

**Table 2** Stability over time of classification into 'regional damage progression' groups at 0-2 years versus 2-5 years of the disease course.

N (%) is shown for all categories, based on all available patients. Bold numbers show the percentage of patients who are stable over time (i.e. classification did not change over time between early and later in the disease course). Foot= predominantly progression of foot; Hand ≈ Foot= similar progression of hand and foot; Hand= predominantly progression of hand; Non-progressors= patients with no progression.

**Longitudinal relation between the DAS28 and radiographic damage**

On group level there was a longitudinal relation between the DAS28 and radiographic progression which is in line with earlier reports (Table 3, model 1).[6] Model 1 describes the longitudinal relation between disease activity and radiographic damage, corrected for time and predictive factors. Treatment strategy was not taken into account in this model, because adding this variable to the model did not influence the relation between disease activity and radiographic damage.

In model 2 predominantly foot progression (i.e. predominantly foot progression vs. other types of progression) was added as independent variable together with an interaction term of this variable and DAS28. Predominantly foot progression influences the relation between DAS28 and radiographic progression, i.e. predominantly foot progressors showing more (change in) radiographic progression at the same (change in the) DAS28 as compared to the other patient groups (Table 3, model 2). In other words, in predominantly foot progressors disease activity assessed by DAS28 seems to be an underestimation as compared to DAS28 in the other 'regional damage progression' groups.

On the group level, joint counts for the feet were not statistically significantly independently related to progression of radiographic damage, but in the predominantly foot progressors the TJC ($p<0.0001$) and SJC of the feet ($p<0.001$) were longitudinally related to radiographic progression (Table 3, model 3 and 4).

| Model | Variable | Beta | 95%CI | p |
|---|---|---|---|---|
| 1 | Intercept | -1.8 | -3.6 - 0.1 | .071 |
| | Time | 1.2 | 0.2 - 2.2 | **.016** |
| | $Time^2$ | -0.2 | -0.4 - 0.01 | .067 |
| | SHS baseline | 0.3 | 0.2 - 0.4 | **<.0001** |
| | SHS baseline*time | -0.1 | -0.1 - -0.02 | **.006** |
| | RF-positive | 1.0 | 0.1 - 1.9 | **.022** |
| | RF-positive*time | 0.1 | -0.3 - 0.4 | .666 |
| | DAS28 | 0.5 | 0.2 - 0.8 | **.002** |
| | SHS total t-1 | 1.1 | 1.0 - 1.1 | **<.0001** |
| 2 | Intercept | -1.0 | -3.2 - 1.1 | .340 |
| | Time | 1.0 | -0.1 - 2.1 | .065 |
| | $Time^2$ | -0.1 | -0.3 - 0.01 | .194 |
| | SHS baseline | 0.4 | 0.2 - 0.5 | **<.0001** |
| | SHS baseline*time | -0.1 | -0.1 - -0.01 | **.015** |
| | RF-positive | 0.7 | -0.4 - 1.7 | .204 |
| | RF-positive*time | 0.1 | -0.3 - 0.5 | .522 |
| | DAS28 | 0.3 | -0.1 - 0.6 | .156 |
| | SHS total t-1 | 1.1 | 1.0 - 1.1 | **<.0001** |
| | Foot progressors | -2.1 | -4.7 - 0.5 | .120 |
| | DAS28*foot progressors | 1.2 | 0.6 - 1.9 | **.0001** |
| 3 | Intercept | -1.8 | -3.9 - 0.3 | .089 |
| | Time | 1.2 | 0.1 - 2.2 | **.030** |
| | $Time^2$ | -0.2 | -0.3 - 0.04 | .111 |
| | SHS baseline | 0.4 | 0.2 - 0.6 | **<.0001** |
| | SHS baseline*time | -0.1 | -0.1 - -0.03 | **.006** |
| | RF-positive | 0.7 | -0.3 - 1.7 | .198 |
| | RF-positive*time | 0.1 | -0.3 - 0.5 | .515 |
| | DAS28 | 0.5 | 0.1 - 0.8 | **.011** |
| | SHS total t-1 | 1.1 | 1.0 - 1.1 | **<.0001** |
| | TJCfeet | -0.1 | -0.3 - 0.1 | .286 |
| | Foot progressors | 0.4 | -1.1 - 1.9 | .593 |
| | TJCfeet*foot progressors | 0.8 | 0.4 - 1.1 | **<.0001** |
| 4 | Intercept | -2.0 | -4.1 - 0.1 | .061 |
| | Time | 1.3 | 0.2 - 2.4 | **.020** |
| | $Time^2$ | -0.2 | -0.4 - 0.03 | .088 |
| | SHS baseline | 0.4 | 0.2 - 0.6 | **<.0001** |
| | SHS baseline*time | -0.1 | -0.1 - -0.02 | **.007** |
| | RF-positive | 0.7 | -0.3 - 1.8 | .154 |
| | RF-positive*time | 0.1 | -0.3 - 0.5 | .649 |
| | DAS28 | 0.5 | 0.1 - 0.8 | **.011** |
| | SHS total t-1 | 1.1 | 1.0 - 1.1 | **<.0001** |
| | SJCfeet | -0.1 | -0.3 - 0.2 | .627 |
| | Foot progressors | 0.9 | -0.5 - 2.4 | .214 |
| | SJCfeet*foot progressors | 0.7 | 0.4 - 1.1 | **.0001** |

**Table 3** Longitudinal relation of radiographic damage and clinical variables over 5 years.

**Table 3** - continued
Models are based on longitudinal (mixed model) autoregressive analysis (i.e. value for the outcome variable was adjusted for the outcome value at the previous time point), modelling change (progression) scores calculated per time interval. The regression coefficient for the time varying independent variables in this model can be interpreted in terms of a cross-sectional relationship, as well as a longitudinal relationship.
SHS= SharpvanderHeijde score; RF= rheumatoid factor; DAS28= disease activity score based on 28 joint count; SHS total t-1= SharpvanderHeijde score at previous time point; Foot progressors= patients with predominantly foot progression; TJCfeet= tender joint count of the feet, based on 10 joints; SJCfeet= swollen joint count of the feet, based on 10 joints; SHS baseline*time= interaction of time with SHS baseline; RF-positive*time= interaction of time with RF-positive; SJCfeet*foot progressors= interaction foot progressors with SJC feet.

To better understand these modifying effects by the 'regional damage progression' group, stratified analyses for the 'regional damage progression' groups of joint involvement were performed. These analyses showed that one unit increase in DAS28 is associated with 0.1 to 1.5 SHS units increase; this effect is largest in the predominantly foot progression group ($p<0.001$) when compared to the other groups (Table 4; in Figure 1 an example patient, with a predefined DAS28 course and simulated radiographic progression, is shown for all 'regional damage progression' groups).

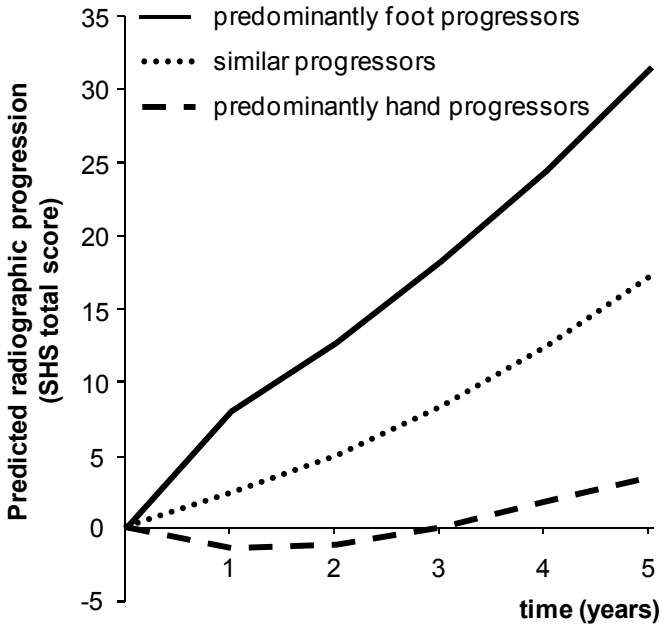


**Figure 1.** Prediction of radiographic progression for 'regional damage progression' groups at the same values of DAS28 (i.e. 5.5 at baseline, 2.6 at 1 until 4 years, and 3.2 at 5 years), based on longitudinal (mixed model) regression, Table 3 - model 2. The solid line for predominantly foot progressors; the dotted line for similar progressors; the dashed line for predominantly hand progressors.

Further it was found that a change in the TJC of feet had an influence on radiographic progression (i.e. higher radiographic progression) in the predominantly foot progressors ($p=0.059$), contrary to the other groups; a similar effect was found for SJC ($p=0.16$) (Table 4).

| Stratified analysis | Variable | Beta | 95%CI | p |
|---|---|---|---|---|
| Predominantly foot | DAS28 | 1.5 | 0.7 - 2.3 | **.0004** |
| Similar | DAS28 | 0.5 | 0.1 - 1.0 | **.030** |
| Predominantly hand | DAS28 | 0.1 | -1.1 - 1.3 | .923 |
| Predominantly foot | DAS28 | 1.3 | 0.4 - 2.1 | **.004** |
| | TJCfeet | 0.4 | -0.01 - 0.7 | .059 |
| Similar | DAS28 | 0.6 | 0.1 - 1.1 | **.026** |
| | TJCfeet | -0.1 | -0.3 - 0.2 | .571 |
| Predominantly hand | DAS28 | 0.2 | -1.1 - 1.6 | .729 |
| | TJCfeet | -0.2 | -0.9 - 0.5 | .599 |
| Predominantly foot | DAS28 | 1.3 | 0.5 - 2.2 | **.002** |
| | SJCfeet | 0.3 | -0.1 - 0.8 | .164 |
| Similar | DAS28 | 0.5 | -0.02 - 1.0 | .058 |
| | SJCfeet | 0.1 | -0.2 - 0.3 | .712 |
| Predominantly hand | DAS28 | 0.2 | -1.1 - 1.4 | .785 |
| | SJCfeet | -0.3 | -1.2 - 0.7 | .568 |

**Table 4** Stratified analysis for influence of 'regional damage progression' groups on longitudinal relation (Table 4, model 1) and stratified analysis for influence on TJC and SJC of feet.
For the subgroup no progression no stratified analyses could be performed, due to no variation in radiographic progression as dependent variable (all scores are zero). Predominantly foot= predominantly foot progression, predominantly hand= predominantly hand progression; similar= similar progression of hand and foot; DAS28= disease activity score based on 28 joint count; TJCfeet= tender joint count of the feet, based on 10 joints; SJCfeet= swollen joint count of the feet, based on 10 joints.

Furthermore, these analyses showed that DAS28 underestimates the actual disease activity in the predominantly foot progressors (Beta=1.5, 95%CI 0.7-2.3, p=0.0004), whereas DAS28 overestimates the actual disease activity in predominantly hand progressors (Beta=0.1, 95%CI -1.1-1.3, p=0.93). However, including TJC or SJC of the feet only partially solves this problem of under- and overestimation; Beta's for DAS28 in predominantly foot progressors changed in both analyses into 1.3, this was 0.2 in predominantly hand progressors (Table 4).

## DISCUSSION

In RA patients with mainly involvement of the feet, DAS28 underestimates actual disease activity and the expected joint damage. This phenomenon is especially evident during the first 2 years of the disease.
Currently, DAS28 is the most used disease activity index and a validated measurement on group level and therefore often used in clinical trials as outcome measurement. However, there are some drawbacks using DAS28 as a disease activity index in general, also on the group level: a simple calculation is not possible and DAS28 gives no clinical insight into its

individual components, i.e. several combinations of the individual components are possible at the same score.[3, 7, 10] In addition, when evaluating disease activity at the individual patient level, an important issue is that joints of feet are not included in DAS28.[3, 7, 17]
For use in individual patients, the absence of assessment of feet joints leads to a lack of accuracy for remission (which is an important aim in tight control strategies).[18, 19] Our results showed that in predominantly foot progressors, joint counts for feet were independently related to radiographic progression. So DAS28 does not capture the influence of feet involvement on radiographic progression for patients with predominantly feet involvement. These problems also apply to other disease activity indices which neither take into account the joints of the feet, like the SDAI and CDAI.[2]
Substantial numbers of patients with either predominantly hand or feet involvement are present early in RA disease course and also later on. Thirty-nine to 51% of the patients in the 'regional damage progression' groups did not change over time to another group. This suggests that the pattern of radiographic damage is relatively stable over time and seems (partly) a patient characteristic and less a time varying disease characteristic.
For comparison of groups in randomised clinical studies this 'regional damage progression' is probably less important, because outcome parameters are evaluated on group level, in contrast to tight control strategies in which treatment strategy is based on the individual patient parameters.
In RA patients with predominantly foot progression, the (change in) DAS28 underestimates the (change in) disease activity (especially during the first 2 years of the disease, including the window of opportunity) and the expected joint damage. This could particularly be a problem in tight control strategies using the DAS28 as monitoring instrument, aimed at remission or low disease activity definition.[3, 5] For follow-up of individual patients, assessment of all joints frequently involved in RA seems indicated. If feet are involved in the individual patient, one should be aware that the DAS28 might underestimate the actual disease activity However, when then including the SJC or TJC of the feet to the DAS28 this underestimation only partly disappears. Given the imperfect relation of disease activity and radiographic progression, regular assessments of radiographs of hands and feet still seem required. Especially when aiming for low disease activity states or remission, our advice, would be to regularly check also the joints of the feet clinically as well as radiographically, particularly early in the disease, to detect predominantly foot progressors and interpret disease activity results as assessed with DAS28 or other indices excluding joints of feet with caution.
In conclusion, in RA patients with predominantly foot problems, the DAS28 underestimates the actual disease activity (especially during the first 2 years of the disease) and the expected joint damage. This could particularly be a problem in tight control strategies, using DAS28 (or another disease activity index based on 28 joints) as monitoring parameter aiming at low disease activity or remission. For follow-up of individual patients, assessment of all joints frequently involved in RA seems indicated, especially early in the disease course.

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## REFERENCES


1. Prevoo ML, van 't Hof MA, Kuper HH, et al. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38:44-8.
2. Aletaha D, Smolen JS. The Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI) to monitor patients in standard clinical care. Best Pract Res Clin Rheumatol 2007;21:663-75.
3. Bakker MF, Jacobs JW, Verstappen SM, et al. Tight control in the treatment of rheumatoid arthritis: efficacy and feasibility. Ann Rheum Dis 2007;66 Suppl 3:iii56-60.
4. Rantalaiho V, Korpela M, Laasonen L, et al. Early combination disease-modifying antirheumatic drug therapy and tight disease control improve long-term radiologic outcome in patients with early rheumatoid arthritis: the 11-year results of the Finnish Rheumatoid Arthritis Combination Therapy trial. Arthritis Res Ther 2010;12:R122.
5. Schipper LG, van Hulst LT, Grol R, et al. Meta-analysis of tight control strategies in rheumatoid arthritis: protocolized treatment has additional value with respect to the clinical outcome. Rheumatology (Oxford) 2010;49:2154-64.
6. Welsing PM, Landewe RB, van Riel PL, et al. The relationship between disease activity and radiologic progression in patients with rheumatoid arthritis: a longitudinal analysis. Arthritis Rheum 2004;50:2082-93.
7. van der Heijde DM, Jacobs JW. The original "DAS" and the "DAS28" are not interchangeable: comment on the articles by Prevoo et al. Arthritis Rheum 1998;41:942-5.
8. Leeb BF, Haindl PM, Maktari A, et al. Disease Activity Score-28 Values Differ Considerably Depending on Patient's Pain Perception and Sex. J Rheumatol 2007.
9. Makinen H, Kautiainen H, Hannonen P, et al. Disease activity score 28 as an instrument to measure disease activity in patients with early rheumatoid arthritis. J Rheumatol 2007;34:1987-91.
10. Fiehn C, Kessler S, Drexler W, et al. Patients with active rheumatoid arthritis but only few tender and swollen joints: a subgroup with impaired short term outcome. Rheumatol Int 2009;29:655-61.
11. Hulsmans HM, Jacobs JW, van der Heijde DM, et al. The course of radiologic damage during the first six years of rheumatoid arthritis. Arthritis Rheum 2000;43:1927-40.
12. Verstappen SM, Jacobs JW, van der Veen MJ, et al. Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open label trial). Ann Rheum Dis 2007;66:1443-9.
13. 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.
14. van der Heijde DM, van Riel PL, Nuver-Zwart IH, et al. Effects of hydroxychloroquine and sulphasalazine on progression of joint damage in rheumatoid arthritis. Lancet 1989;1:1036-8.
15. van Gestel AM, Prevoo ML, van 't Hof MA, et al. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism Criteria. Arthritis Rheum 1996;39:34-40.
16. Aletaha D, Funovits J, Breedveld FC, et al. Rheumatoid arthritis joint progression in sustained remission is determined by disease activity levels preceding the period of radiographic assessment. Arthritis Rheum 2009;60:1242-9.
17. Landewe R, van der Heijde D, van der Linden S, et al. Twenty-eight-joint counts invalidate the DAS28 remission definition owing to the omission of the lower extremity joints: a comparison with the original DAS remission. Ann Rheum Dis 2006;65:637-41.
18. van der Leeden M, Steultjens MP, van Schaardenburg D, et al. Forefoot disease activity in rheumatoid arthritis patients in remission: results of a cohort study. Arthritis Res Ther 2010;12:R3.
19. Makinen H, Kautiainen H, Hannonen P, et al. Is DAS28 an appropriate tool to assess remission in rheumatoid arthritis? Ann Rheum Dis 2005;64:1410-3.

Chapter 10

# The relation between cartilage biomarkers (C2C, C1,2C, CS846, and CPII) and the long-term outcome of RA patients within the CAMERA trial

On behalf of the Utrecht Arthritis Cohort study group; biomarker analyses were performed at the Joint Disease Laboratory, Shriners Hospitals for Children, Montreal, Canada

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*Submitted for publication*

## ABSTRACT

### Objective

To investigate whether serum biomarker levels of C2C, C1,2C, CS846, and CPII can predict the long-term course of disease activity and radiographic progression early in the disease course of RA.

### Methods

In patients within the CAMERA trial, levels of biomarkers were evaluated at baseline and 1 year of treatment. Relations of (changes in) biomarker values with the mean yearly radiographic progression rate and mean disease activity over 5 years were evaluated using regression analysis. The added predictive value of biomarkers over established predictors for long-term outcome was analyzed by multiple linear regression analysis.

### Results

Of 133 patients, serum samples were available at baseline and 1 year of treatment. In the regression analysis C1,2C at baseline, the change in C2C, C1,2C, and the sum of the standardized changes in C2C+C1,2C scores were statistically significantly associated with the mean yearly radiographic progression rate; the change in CPII was associated with the mean disease activity over 5 years of treatment. In the multiple linear regression analysis only the change in C1,2C was of added predictive value ($p=0.004$) for radiographic progression. Explained variances of models for radiographic progression and disease activity were low (0.28 and 0.34, respectively) and the biomarkers only marginally improved the explained variance.

### Conclusion

The change in C1,2C in the first year after onset of RA has a small added predictive value for disease severity over 5 years, but the predictive value of this biomarker combined with current predictive factors is too small to be of use for individual patients.

## INTRODUCTION

Biomarkers are molecules or fragments that are released into biologic fluids during the process of tissue turnover and, for rheumatoid arthritis (RA), are considered to be indicative of degradation or synthesis of cartilage, bone, and synovial tissue.[1] Several serum biomarkers are on the market, including those provided by IBEX (Montreal, Canada); C2C, C1,2C, CS846, and CPII.[2-5] These biomarkers might be good candidates since they directly reflect the bone and cartilage turnover rate in the (affected) joints of patients with RA. The two markers for collagen degradation originate from type II collagen (C2C) and from type I as well as type II collagen (C1,2C), reflecting cartilage and bone degradation. The marker for turnover originated from proteoglycan aggrecan (CS846) and the marker for synthesis of type II procollagen (CPII).

Earlier research with these biomarkers showed no consistent results regarding the predictive value for the long-term outcomes in (early) RA. Only six publications described the relation of (one of) the above biomarkers with (long-term) radiographic (Table 1) or clinical (Table 2) outcome in RA.[6-11] The relation between these biomarker values and radiographic progression is inconsistent; some studies show a higher value in case of higher radiographic progression,[7, 9, 11] whereas others show a lower value in case of higher radiographic progression [8] or show no association at all.[7-11] The same holds true for the relation between these biomarker values and disease activity over time.[9]

Because of these conflicting results and the limited available literature on the association between these biomarkers and clinical and radiographic progression, the aim of this study was to investigate whether C2C, C1,2C, CS846, and CPII determined early in the disease can predict the long-term radiographic and/or clinical outcome in patients with early RA.

## PATIENTS AND METHODS

Patients included in this study were participants in the two-year randomized open-label prospective multi-centre treatment strategy trial (Computer Assisted Management in Early Rheumatoid Arthritis, CAMERA [12]). In the CAMERA study, patients were randomly assigned to either an intensive tightly controlled MTX-based treatment strategy based on computer guided monthly predefined response criteria or to a conventional MTX-based treatment strategy based on regular clinical practice with three-monthly visits. All patients fulfilled the 1987 revised American College of Rheumatology (ACR) criteria for RA.[13] At study entry, all patients had a disease duration of less than 1 year and were DMARD- and glucocorticoid-naïve. The medical ethics committees of all participating hospitals approved the study, and all patients gave written informed consent before entering the trial.

| Author | Population | n | Biomarker | Classification | Results |
|---|---|---|---|---|---|
| Syversen et al.[10] | RA ≤4yr | 136 | C2C (baseline serum) | SHS rapid>1 vs. slow<1 (radiographic progression per yr, progression change baseline - 5 or 10yrs) | ns |
| Mullan et al.[9] | RA | 45 | C2C (baseline,1,3,6,9,12m serum) | | C2C ↑ at 1,3m |
| | PsA (mean 11yrs, DAS28>3.2) | 17 | C1,2C | SHS rapid>1.5 vs. slow<1.5 (radiographic progression at 1yr) | C1,2C ↑ at 1,3m |
| | | | CPII | | ns |
| | | | ΔCOL (ΔC2C+ΔC1,2C+ΔCPII) | | ΔCOL ↑ at 1,3,6,9m |
| Verstappen et al.[11] | RA ≤1yr | 87 | C2C (1,2,3,4yr serum) | | C2C ↑ |
| | | | C1,2C | 66th= SHS>7.4 vs. 33rd percentile= SHS<2.3 (radiographic progression over 4yrs) | C1,2C ↑ |
| | | | CS846 | | CS846 ↑ |
| | | | CPII | | ns |
| Ishiguro et al.[7] | RA (mean 10yrs) | 63 | C2C (knee SF) | mild vs. moderate vs. severe RA | ns |
| | | | CS846 | mild vs. moderate RA | CS846 ↓ |
| | | | CPII | mild vs. moderate vs. severe RA (Larsen score: 0&1=mild, 2&3=moderate, 4&5=severe) | ns |
| Mansson et al.[8] | RA<2yr | 18 | CS846 (baseline serum) | rapid vs. slow hip joint radiographic progression | CS846 ↓ |
| | | | CPII | (Larsen score: rapid=46, slow=4 at 2yrs) | ns |

**Table 1** Overview of the literature on the (significant) relation between biomarker and radiographic progression.
n= number of patients investigated in the studies; RA= rheumatoid arthritis; PsA= psoriatic arthritis; yr= year; yrs= years, DAS28= disease activity score based on 28 joints; m= months; SF= synovial fluid; SHS= SharpvanderHeijde score; ns= not significant.

| Author | Population | n | Biomarker | Classification | Results |
|---|---|---|---|---|---|
| Mullan et al.[9] | RA | 45 | C2C (baseline,1,3,6,9,12m serum) | DAS28 responders vs. non responders (at 3m) | C2C ↓ |
| | PsA | 17 | C1,2C | (responder: ≥0.6 improvement & DAS28≤5.1, | ns |
| | (mean 11yrs, | | CPII | non-responder: <0.6 improvement OR DAS28>5.1) | ns |
| | DAS28>3.2) | | ΔCOL (ΔC2C+ΔC1,2C+ΔCPII) | | ΔCOL ↓ |
| Mullan et al.[9] | RA | 45 | C2C (baseline,1,3,6,9,12m serum) | | C2C ↓ at 1m |
| | PsA | 17 | C1,2C | remission vs. no remission | C1,2C ↓ at 1m |
| | (mean 11yrs, | | CPII | (remission= DAS28<2.6 at 6m) | ns |
| | DAS28>3.2) | | ΔCOL (ΔC2C+ΔC1,2C+ΔCPII) | | ΔCOL ↓ change 1m |

**Table 2** Overview of the literature on the (significant) relation between biomarker and the disease activity.
n= number of patients investigated in the studies; RA= rheumatoid arthritis; PsA= psoriatic arthritis; yrs= years, DAS28= disease activity score based on 28 joints; m= months; SF= synovial fluid; ns= not significant.

From all available patients, serum samples were collected at baseline (before treatment) and 1 year after inclusion into the study. Serum samples were frozen as soon as possible after blood collection and stored at -20°C until analysis (analysis shortly after all 1 year samples were obtained). Since the trial was performed according to general clinical practice as much as possible, sample collection was not restricted to fasting conditions.

**Biomarker analyses**

For this study, only samples that had not been thawed before were used. For all biomarkers, ELISAs were performed according to manufacturer's instructions (IBEX Montreal, Canada).
The C2C serum ELISA detects a cartilage specific collagen type II collagenase cleavage neoepitope.[2] The C1,2C ELISA detects a collagenase generated collagen type I and II cleavage neoepitope.[3] The CS846 ELISA detects an epitope on chondroitin sulfate of newly formed large aggrecan molecules.[4] The CPII ELISA recognizes epitopes of the pro-peptide of collagen type II reflecting synthesis.[5]
Values of all four biomarkers were log transformed to obtain normal distributions. Additionally, seven extreme outliers derived from C2C, CS846, and CPII (based on visual inspection) were excluded for analysis.

**(Long-term) Outcome measurements**

The long-term outcome of RA patients was determined by the radiographic joint progression and by the mean disease activity over 5 years of treatment. To assess radiographic joint progression, radiographs of hand and feet were made at baseline and every subsequent year. Radiographs were independently scored according to the SharpvanderHeijde score (SHS) [14] by 2 readers, blinded to clinical information. The mean yearly radiographic progression rate between baseline and 5 years was used as outcome measure. For this rate, if 5 year radiographs were not available, the mean of the measurements between 4 and 6 years were used, or scores at 4 or 6 years, depending on the data available. Since scores were not normally distributed, the log transformed progression rate (log rate +1) was used.
The mean disease activity over 5 years was determined by calculating a time-averaged value of the DAS28 [15] using the area under the curve (AUC) from baseline until 5 years after treatment. If more than 2 yearly time points were missing, no time-averaged DAS28 could be calculated.

The early response has been shown to be a predictor for long-term outcome [16] and was therefore also taken into account in the analysis. The DAS28 at baseline and 6 months was used to calculate the early EULAR response. Patients were classified as good-, moderate- or non-responders based on their early (change in) disease activity. Good-responders should have a DAS28 score ≤3.2 at 6 months and an improvement from baseline >1.2; non-responders a DAS28 score >5.1 and an improvement between 0.6 and 1.2 or only an

improvement of ≤0.6. Patients with moderate-response had a response in between the good- and non-responders.

**Statistical analyses**

The change in biomarker values was calculated by subtracting the baseline biomarker value from the 1-year value for all biomarkers. Furthermore, sum scores of (changes in) markers representing synthesis (CS846 and CPII) and sum scores of (changes in) markers for degradation (C2C and C1,2C) were calculated. Finally, the ratio of (the sum scores of) synthesis and degradation markers were calculated. Because ranges of individual biomarker values differ, Z-scores (calculated by subtracting the average value from the individual value divided by the standard deviation) were used for the sum and ratio scores.

The relation between the individual (change, sum, and ratio of) biomarker values and long-term outcome (i.e. mean yearly radiographic progression rate and time-averaged DAS28) was investigated by linear regression analysis, adjusting for the treatment strategy (i.e. intensive tightly controlled or conventional MTX-based strategy).

Secondly, to investigate whether biomarker values were of additional value over already known baseline predictors (rheumatoid factor (RF) and joint damage or disease activity at baseline, respectively), multiple linear regression analysis was used, adjusting for treatment strategy. The sum and ratio scores were only considered in the analysis when the individual biomarkers had a significant association with the outcome in the initial analysis. In the final model also the early (6 month) EULAR response was added, by means of two dummy variables (good- and moderate-response, with non-response as reference category).

The statistical software SPSS 15.0 was used for the analyses. A p-value <0.05 was considered statistically significant.

**RESULTS**

Of 133 patients within the CAMERA trial, unthawed serum samples were available at baseline and 1 year of treatment. Of these patients, 75 had been treated according to an intensive tightly controlled MTX-based strategy and 58 patients according to a conventional MTX-based strategy. For 5 patients no mean yearly radiographic progression rate could be calculated due to missing scores. For 11 patients no time-averaged DAS28 could be calculated since more than two DAS28 scores were missing. Baseline characteristics of patients with missing data were not statistically significantly different from those of patients with complete data. Clinical characteristics and biomarker data of the patients are shown in Table 3.

| Characteristic | | n = 133 |
|---|---|---|
| Female gender (%) | | 87 (65) |
| Age (years) | | 53 (14) |
| RF-positivity (%) | | 87 (65) |
| Baseline DAS28 | | 5.6 (1.0) |
| Baseline joint damage | | 0.0 (0.0-0.0) |
| EULAR good responders (%) | | 50 (38) |
| EULAR moderate responders (%) | | 58 (44) |
| EULAR no responders (%) | | 24 (18) |
| Time-averaged DAS28 | | 3.0 (0.9) |
| Radiographic progression rate | | 1.0 (0.0-3.4) |
| C2C (ng/ml) | *baseline* | 90 (71-124) |
| | *1 year* | 86 (70-109) |
| C1,2C (ng/ml) | *baseline* | 359 (286-427) |
| | *1 year* | 349 (269-415) |
| CS846 (ng/ml) | *baseline* | 100 (68-155) |
| | *1 year* | 113 (69-183) |
| CPII (ng/ml) | *baseline* | 335 (207-551) |
| | *1 year* | 436 (220-613) |

**Table 3** Clinical and biomarker characteristics obtained at baseline and follow-up of all available patients.

Mean (SD) is shown for age and (baseline and time-averaged) DAS28; median (IQR) is shown for all other (non-normally distributed) continuous variables. For all categorical variables number (%) of patients is shown. The EULAR response was determined after 6 months of treatment; time-averaged DAS28 and radiographic progression rate were calculated over 5 years of treatment; all other variables were determined at baseline unless otherwise stated.

In the analyses correcting for treatment strategy, C1,2C at baseline, the change in C2C and in C1,2C, and (consequently) the sum of the standardized changes in C2C+C1,2C levels were statistically significantly related to the mean yearly radiographic progression rate (all $p<0.05$, Table 4). Only the change in CPII levels was related to time-averaged DAS28 ($p=0.03$, Table 4).

| | | Long-term outcome (5 years after treatment) | | | | | |
|---|---|---|---|---|---|---|---|
| | | *yearly radiographic progression rate* | | | *time-averaged DAS28* | | |
| Biomarker | | *n* | *B* | 95%CI | *n* | *B* | 95%CI |
| C2C | baseline | 126 | .08 | -.28 to .44 | 120 | .11 | -.25 to .47 |
| | 1 year | 126 | -.23 | -.67 to .20 | 120 | .18 | -.25 to .61 |
| | change | 126 | **-.59** | **-1.14 to -.03** | 120 | .04 | -.52 to .60 |
| C1,2C | baseline | 126 | **.47** | **.001 to .95** | 120 | .10 | -.40 to .60 |
| | 1 year | 127 | .14 | -.36 to .65 | 121 | .22 | -.29 to .73 |
| | change | 126 | **-1.00** | **-1.80 to -.20** | 120 | .33 | -.52 to 1.18 |
| CS846 | baseline | 127 | -.06 | -.27 to .16 | 121 | -.08 | -.29 to .14 |
| | 1 year | 126 | -.07 | -.29 to .15 | 120 | -.03 | -.26 to .20 |
| | change | 126 | -.01 | -.23 to .21 | 120 | .05 | -.18 to .28 |
| CPII | baseline | 124 | .14 | -.07 to .35 | 118 | -.05 | -.26 to .17 |
| | 1 year | 125 | .13 | -.09 to .34 | 119 | .10 | -.12 to .31 |
| | change | 122 | -.07 | -.34 to .20 | 122 | **.30** | **.02 to .57** |
| ZC2C+ZC1,2C | baseline | 125 | .07 | -.02 to .17 | | | |
| | 1 year | 126 | .01 | -.11 to .08 | | | |
| | change | 126 | **-.13** | **-.22 to -.04** | | | |

**Table 4** Association between biomarker values with the long-term outcome measures.
Biomarkers with B (95%CI) values which are shown in **Bold** type have a p value <0.05 and have been included in the multiple regression analyses. Biomarkers values were determined at baseline, at 1 year, and the change between 1 year and baseline. Next to that also sum and ratio scores (based on Z-values) were determined when individual biomarkers had a significant association with the outcome in the initial analysis.

In the multiple linear regression analyses the change in C1,2C and the sum of the standardized changes in C2C+C1,2C levels were significantly related (p=0.004 and p=0.02, respectively) to mean yearly radiographic progression rate in addition to RF, baseline joint damage, and early (6 month) EULAR response. However, when including both changes in biomarkers values in the analysis, they were no longer statistically significant (p=0.13 and p=0.94, respectively). The change in C1,2C was chosen for the final model because this biomarker had the highest standardized beta and the final model had the highest R-square when compared to the sum of the standardized changes in C2C+C1,2C levels; furthermore including only one biomarker instead of two is more efficient.
The R-square of the final model increased from 0.23 without biomarker to 0.28 including the change score of C1,2C (Table 5). When early response was not included, results were comparable and the R-square of the model changed from 0.20 to 0.27 if C1,2C was added. The standardized beta's showed that the influence of the biomarkers on prediction of mean yearly radiographic progression rate was much smaller than for instance the predictive influence of baseline joint damage (standardized beta= -0.24 vs. 0.44, respectively, Table 5).

| Item | B | 95%CI | standardized Beta | p | R-square |
|---|---|---|---|---|---|
| Intercept | .54 | .12 to .96 | | .013 | |
| Treatment strategy | .13 | -.16 to .43 | .08 | .375 | .000 |
| RF positive | .29 | -.02 to .60 | .15 | .063 | .029 |
| Baseline joint damage | .09 | .06 to .13 | .44 | **.000** | .211 |
| EULAR good-response* | -.36 | -.78 to .07 | -.20 | .100 | |
| EULAR moderate-response* | -.13 | -.52 to .27 | -.07 | .534 | .229 |
| C1,2C change 1yr – baseline | -1.11 | -1.87 to -.36 | -.24 | **.004** | .283 |

**Table 5** Added predictive value of biomarkers over already known predictors for mean yearly radiographic progression rate over 5 years of treatment.

* EULAR non-response was used as reference category

The change score of CPII was not statistically significantly related (p=0.18) to time-averaged DAS28. The R-square of the model increased marginally from 0.32 without biomarker to 0.34 including this biomarker (Table 6). When early response was not included in the model, the R-square increased from 0.13 to 0.21 by adding the biomarker but CPII was still not statistically significantly related to time-averaged DAS28. The standardized beta's also showed that the influence of the biomarkers was much smaller than those of RF, baseline disease activity, and early EULAR response (Table 6).

| Item | B | 95%CI | standardized Beta | p | R-square |
|---|---|---|---|---|---|
| Intercept | 1.90 | .99 to 2.81 | | .000 | |
| Treatment strategy | -.29 | -.62 to .03 | -.16 | .076 | .076 |
| RF positive | .35 | .02 to .68 | .18 | **.040** | .098 |
| Baseline disease activity | .25 | .10 to .40 | .30 | **.001** | .169 |
| EULAR good-response* | -.84 | -1.30 to -.37 | -.46 | **.001** | |
| EULAR moderate-response* | -.19 | -.64 to .25 | -.11 | .393 | .322 |
| CPII change 1yr – baseline | .18 | -.08 to .43 | .12 | .178 | .335 |

**Table 6** Added predictive value of biomarkers over already known predictors for time-averaged disease activity (DAS28) over 5 years of treatment.

* EULAR non-response was used as reference category

## DISCUSSION

The results show that some of the biomarkers have a small predictive value for long-term outcome in early RA, but clearly less compared to established predictors. Only the change in C1,2C, the sum of the standardized changes in C2C+C1,2C levels, and the change in CPII were of added value for respectively the mean yearly radiographic progression rate and the time-averaged DAS28. However, the explained variance of the final prediction models was

low and therefore not useful for clinical practice and both biomarkers only increased the explained variance marginally (and not statistically significant for CPII).

Possible explanations of not finding a relation with all biomarkers are the small variances in outcome regarding the radiographic progression due to the low radiographic scores, despite the 5 years follow-up. When comparing other investigations of the four biomarkers (see Table 1 and 2) with our own data, patients in the other studies had higher radiographic scores at baseline and had on average also higher disease durations (varying from 1 up to 10 years RA). The available radiographic scores at baseline of the evaluated studies range from 6.8 - 60 for SHS (mean) and 2 - 7 for the Larsen score (median) compared to 0 SHS (median) in our study. Verstappen et al. [11] investigated the same biomarkers comparing fast (>7.3 SHS units/year) and slow progressors (<2.3 SHS units/year) and found significant differences in biomarkers values, except for CPII, in another cohort of patients with early RA. However, these slowest progressors (calculated over 4 years) in this previous study are comparable to the patients with the fastest progression ($66^{th}$ tertile >2.4 SHS units/year) in our present study (calculated over 5 years). Important to consider is that due to improved treatment (strategies) progression rate nowadays in the western community will hardly exceed the progression rate of the present cohort. This progress in treatment effectiveness and tight control strategies titrating treatment to the disease course of an individual patient might counterbalance the predictive value of biomarkers in prediction of disease outcome. However, it should not be ignored that also in the previous studies with higher radiographic progression rates the relation of these biomarkers with outcome was not straightforward (see Table 1).

In a post-hoc analysis evaluating all sum and ratio scores of synthesis and degradation markers (instead of only the ones when the individual biomarker had a significant association), no significant associations were seen with both the mean yearly radiographic progression rate and the time-averaged DAS28 over 5 years of treatment; this also applied for the multiple linear regression analysis (data not shown). The possible influence of age and gender on the biomarker values was also investigated with multiple linear regression analyses; adding these variables to the models did not change the results (data not shown).

The direction of the relation between the biomarkers and the mean yearly radiographic progression rate and time-averaged DAS28 was not anticipated. An increase in C1,2C during 1 year of treatment, which indicates more connective tissue degradation, led to lower mean yearly radiographic progression rate, whereas a higher time-averaged DAS28 was reached with an increase in cartilage collagen synthesis as determined by an increase in CPII between baseline and 1 year of treatment. On the other hand, in vitro data reveals that the neoepitope can increase when collagenase activity is blocked.[17] This is because collagenase can cleave the neoepitope that it generates.[3] Also in osteoarthritis (OA) serum CPII increased with progression of OA (Poole et al., unpublished data), similar as in the present study on RA. As in general contrasting relations have been found (Table 1 and 2 and this study), clearly, the nature, origin, and metabolism of these (and other) biomarkers need further investigation.[18]

Based on the present results the investigated markers are not the first choice in predicting long-term outcome in individual patients with early RA. The available studies together with the present results suggest that the role of these markers in predicting long-term outcome is at most modest. They might, on the other hand, be of value for other joint diseases or in distinguishing RA from other arthritis conditions. Significant differences in these biomarkers were reported when comparing RA with psoriatic arthritis,[6] OA,[6, 7] and controls.[8] When investigating the baseline biomarker values of the early RA patients of the CAMERA trial with controls, also significant differences were seen (all $p<0.01$; data not shown). Also for assessment of progression in treatment with anti-TNF these biomarkers appeared of use.[9]
Biomarkers in general might be of value in prediction of the long-term outcome of RA. CTX-II,[19-23] CTX-I,[20, 22] MMP-3,[23, 24] COMP,[25] calprotectin,[26] RANKL,[27] and IL-6 [28] all showed to have a relation with (long-term) radiographic progression and/or the disease activity score. Of all these biomarkers, CTX-II is at present the most frequently used and best performing marker. Recently, a trial demonstrated CTX-II and DAS28 almost equally effective when used to monitor disease activity and in treatment decisions aiming at remission of disease of RA.[29]
In conclusion, the change in C1,2C and CPII in the first year after onset have a small added predictive value for respectively radiographic progression and disease activity over 5 years, though the predictive value is too small to be useful in daily clinical practice.

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## REFERENCES


1. Poole AR, Dieppe P. Biological markers in rheumatoid arthritis. Semin Arthritis Rheum 1994;23:17-31.
2. Poole AR, Ionescu M, Fitzcharles MA, et al. The assessment of cartilage degradation in vivo: development of an immunoassay for the measurement in body fluids of type II collagen cleaved by collagenases. J Immunol Methods 2004;294:145-53.
3. Billinghurst RC, Dahlberg L, Ionescu M, et al. Enhanced cleavage of type II collagen by collagenases in osteoarthritic articular cartilage. J Clin Invest 1997;99:1534-45.
4. Rizkalla G, Reiner A, Bogoch E, et al. Studies of the articular cartilage proteoglycan aggrecan in health and osteoarthritis. Evidence for molecular heterogeneity and extensive molecular changes in disease. J Clin Invest 1992;90:2268-77.
5. Nelson F, Dahlberg L, Laverty S, et al. Evidence for altered synthesis of type II collagen in patients with osteoarthritis. J Clin Invest 1998;102:2115-25.
6. Fraser A, Fearon U, Billinghurst RC, et al. Turnover of type II collagen and aggrecan in cartilage matrix at the onset of inflammatory arthritis in humans: relationship to mediators of systemic and local inflammation. Arthritis Rheum 2003;48:3085-95.
7. Ishiguro N, Ito T, Oguchi T, et al. Relationships of matrix metalloproteinases and their inhibitors to cartilage proteoglycan and collagen turnover and inflammation as revealed by analyses of synovial fluids from patients with rheumatoid arthritis. Arthritis Rheum 2001;44:2503-11.
8. Mansson B, Carey D, Alini M, et al. Cartilage and bone metabolism in rheumatoid arthritis. Differences between rapid and slow progression of disease identified by serum markers of cartilage metabolism. J Clin Invest 1995;95:1071-7.
9. Mullan RH, Matthews C, Bresnihan B, et al. Early changes in serum type II collagen biomarkers predict radiographic progression at one year in inflammatory arthritis patients after biologic therapy. Arthritis Rheum 2007;56:2919-28.
10. Syversen SW, Goll GL, van der Heijde D, et al. Cartilage and bone biomarkers in rheumatoid arthritis: prediction of 10-year radiographic progression. J Rheumatol 2009;36:266-72.
11. Verstappen SM, Poole AR, Ionescu M, et al. Radiographic joint damage in rheumatoid arthritis is associated with differences in cartilage turnover and can be predicted by serum biomarkers: an evaluation from 1 to 4 years after diagnosis. Arthritis Res Ther 2006;8:R31.
12. Verstappen SM, Jacobs JW, van der Veen MJ, et al. Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open label trial). Ann Rheum Dis 2007;66:1443-9.
13. 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.
14. van der Heijde DM, van Riel PL, Nuver-Zwart IH, et al. Effects of hydroxychloroquine and sulphasalazine on progression of joint damage in rheumatoid arthritis. Lancet 1989;1:1036-8.
15. Prevoo ML, van 't Hof MA, Kuper HH, et al. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38:44-8.
16. Bakker MF, Jacobs JWG, Bijlsma JWJ, et al. Early good response to therapy in RA patients predicts a better long-term clinical course and less radiographic joint damage. Arthritis And Rheumatism 2008;58:S764-5.
17. Dahlberg L, Billinghurst RC, Manner P, et al. Selective enhancement of collagenase-mediated cleavage of resident type II collagen in cultured osteoarthritic cartilage and arrest with a synthetic inhibitor that spares collagenase 1 (matrix metalloproteinase 1). Arthritis Rheum 2000;43:673-82.
18. van Spil WE, de Groot J, Lems WF, et al. Serum and urinary biochemical markers for knee and hip-osteoarthritis: a systematic review applying the consensus BIPED criteria. Osteoarthritis Cartilage 2010;18:605-12.
19. Hashimoto J, Garnero P, van der Heijde D, et al. A combination of biochemical markers of cartilage and bone turnover, radiographic damage and body mass index to predict the progression of joint destruction in patients with rheumatoid arthritis treated with disease-modifying anti-rheumatic drugs. Mod Rheumatol 2009;19:273-82.

20. Landewe RB, Geusens P, van der Heijde DM, et al. Arthritis instantaneously causes collagen type I and type II degradation in patients with early rheumatoid arthritis: a longitudinal analysis. Ann Rheum Dis 2006;65:40-4.
21. Marotte H, Gineyts E, Miossec P, et al. Effects of infliximab therapy on biological markers of synovium activity and cartilage breakdown in patients with rheumatoid arthritis. Ann Rheum Dis 2009;68:1197-200.
22. Syversen SW, Haavardsholm EA, Boyesen P, et al. Biomarkers in early rheumatoid arthritis: longitudinal associations with inflammation and joint destruction measured by magnetic resonance imaging and conventional radiographs. Ann Rheum Dis 2010;69:845-50.
23. Young-Min S, Cawston T, Marshall N, et al. Biomarkers predict radiographic progression in early rheumatoid arthritis and perform well compared with traditional markers. Arthritis Rheum 2007;56:3236-47.
24. Visvanathan S, Marini JC, Smolen JS, et al. Changes in biomarkers of inflammation and bone turnover and associations with clinical efficacy following infliximab plus methotrexate therapy in patients with early rheumatoid arthritis. J Rheumatol 2007;34:1465-74.
25. Lindqvist E, Eberhardt K, Bendtzen K, et al. Prognostic laboratory markers of joint damage in rheumatoid arthritis. Ann Rheum Dis 2005;64:196-201.
26. Hammer HB, Odegard S, Syversen SW, et al. Calprotectin (a major S100 leukocyte protein) predicts 10-year radiographic progression in patients with rheumatoid arthritis. Ann Rheum Dis 2010;69:150-4.
27. Gonzalez-Alvaro I, Ortiz AM, Tomero EG, et al. Baseline serum RANKL levels may serve to predict remission in rheumatoid arthritis patients treated with TNF antagonists. Ann Rheum Dis 2007;66:1675-8.
28. Knudsen LS, Klarlund M, Skjodt H, et al. Biomarkers of inflammation in patients with unclassified polyarthritis and early rheumatoid arthritis. Relationship to disease activity and radiographic outcome. J Rheumatol 2008;35:1277-87.
29. van Tuyl LH, Lems WF, Voskuyl AE, et al. Tight control and intensified COBRA combination therapy in early rheumatoid arthritis: 90% remission in a pilot trial. Ann Rheum Dis 2008;67:1574-7.

Chapter 11

# Performance of a multi-biomarker test measuring disease activity in rheumatoid arthritis in the CAMERA study

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## ABSTRACT

### Objective

To evaluate the performance of a multi-biomarker disease activity test (MBDA) and its predictive value for 2-year outcome in an independent early rheumatoid arthritis (RA) patient population.

### Methods

Twenty serum protein biomarkers were measured in serum samples (72 samples at baseline and 48 at 6 months) from the CAMERA study. The MBDA score was calculated using the concentrations of 12 biomarkers (SAA1, IL6, TNFR1, VEGFA, MMP1, YKL40, MMP3, EGF, VCAM1, Leptin, Resistin, and CRP) in a previously trained algorithm. The performance of the MBDA score was evaluated by Pearson correlation (r), AUROC, and (weighted) Kappa compared to DAS28(-CRP) and individual components. Finally, prognostic value of the MBDA score for progression of radiographic joint damage at 2 years was assessed with logistic regression analysis.

### Results

Between 6 and 14 biomarkers were significantly correlated with disease activity variables ($q<0.05$). The MBDA score had a significant correlation with DAS28-CRP ($r=0.73$, $p<0.001$) and an AUROC for distinguishing low from moderate/high disease activity of 0.87 ($p<0.001$). In multivariate analysis the MBDA score was an independent predictor of disease activity measures. The mean (SD) MBDA score decreased significantly from 53 (18) at baseline to 39 (16) at 6 month in response to study therapy ($p<0.0001$).

### Conclusion

The MBDA score performed well in the assessment of disease activity in RA patients in the CAMERA study. Upon further validation, this test could be used to improve currently available disease activity measures and improve patient care and outcomes.

## INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease causing joint pain and destruction of joints, with resulting functional disability.[1] Currently, disease modifying anti-rheumatic drugs (DMARDs) and biologicals that target the autoimmune activation of inflammation are used in treatment of RA.[2-4] When treating RA, it is not only important to start early with treatment, within the so-called window of opportunity,[5] but also to monitor the activity of the disease and the effect of treatment over time and adjust treatment accordingly. This concept, better known as the “tight control principle”, aims specifically to prevent disease progression rather than simply treat the disease.[6-8] First used in the treatment of diabetes (by monitoring blood glucose levels through the measurement of hemoglobin A1C), tight control is defined as a strategy of tailoring treatment to the disease activity of an individual patient. In RA, the ultimate goal of tight control is to achieve a predefined level of remission or low disease activity through frequent monitoring of disease activity and intensifying treatment when not enough improvement is seen until the preset treatment goal is reached.[9] Current recommendations for treatment of RA specify frequent monitoring of disease activity; every month in patients with high disease activity to every 3 months in patients with low disease activity. Drug therapy should be tailored to the individual patient and adjusted appropriately based on disease activity.[8]

One of the studies that examined a tight control strategy was the Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA) trial.[10,11] Subjects with early RA were randomly assigned to either a conventional MTX-based management strategy or a intensive (tight control) MTX-based strategy (using more frequent follow-up and aggressive therapy with MTX according to a strict protocol determined by a computerized decision program based on the disease activity score (DAS28) components) with the aim of reaching remission. After two years of treatment, subjects in the intensive (tight control) strategy group achieved remission more often, faster, and for a longer period of time than subjects receiving conventional MTX-based treatment strategy.

Currently, measurements of disease activity in the clinic usually include symptom assessment, joint counts, individual laboratory tests (e.g. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)) and less frequently radiography.[12] Since RA is polygenic disease that involves complex interactions between many proteins in a biologic network, a multi-biomarker index that captures the numerous biological pathways has the potential for accurately and precisely monitoring of disease activity and be used in a tight control strategy, improving patient outcomes.

Vectra DA™(Crescendo Bioscience, South San Francisco, California), a multi- biomarker test which was developed to evaluate disease activity (MBDA), simultaneously measures 12 proteins that have been shown to be associated with RA disease activity.[13,14] Through monitoring the levels of biomarkers associated with RA disease activity, this test has the potential to facilitate frequent and reliable assessments of disease activity and with that facilitate a tight control treatment strategy.

The purpose of the current study was to evaluate a broad set of serum biomarkers of RA disease activity and to confirm the agreement of the MBDA score algorithm with (clinical) disease activity and its predictive value for 2-year outcome in an independent patient population, the CAMERA study cohort.

## PATIENTS AND METHODS

### Patient Cohort

Serum samples from the CAMERA cohort, a two-year, multicenter, prospective, open-label study from baseline and after six months of treatment were used.[10,11,15] Patients with early RA who met the 1987 revised American College of Rheumatology (ACR) criteria for RA [16] were randomly assigned to one of two treatment strategies: 151 received the intensive tight control (TC) MTX-based treatment strategy and 148 patients received the conventional (CT) MTX-based treatment strategy. Patients visited the outpatient clinic of one of the six rheumatology departments in the region of Utrecht, the Netherlands, from 1999 - 2003. Inclusion criteria consisted of disease duration <1 year and age >16 years. Patients who reported previous use of glucocorticoids or any DMARD or use of cytotoxic or immunosuppressive drugs within a period of 3 months before inclusion were not included in the study.

Every month (TC) or three months (CT) the following clinical variables were assessed: swollen joint count (SJC28, 0-28 joints), tender joint count (TJC28, 0-28 joints), visual analogue scale (VAS) pain (0-100 mm; 100=worst possible pain), VAS general well-being (0-100 mm; 100=worst score), erythrocyte sedimentation rate (ESR, mm/h$^{1st}$), C-reactive protein (CRP, mg/l), morning stiffness (0-180 minutes). DAS28 [17] was calculated, an index for disease activity based on the TJC and SJC of 28 joints, ESR, and a VAS general well-being (VAS-GH). The Health Assessment Questionnaire (HAQ, Dutch version [18]) was assessed every three months. Rheumatoid factor status at baseline was defined as positive or negative.

In the TC strategy dose adjustments were made based on changes in joint counts (TJC and SJC), ESR, and VAS-GH as assessed by a computer decision program. In the CT strategy dose adjustments were made based on the opinion of the individual rheumatologist.

### Laboratory methods

A total of 120 serum samples from the CAMERA study were examined; of these, 72 were collected at baseline and 48 were collected at 6 months. Serum samples were collected in standard separator tubes according to manufacturer's protocol, frozen as soon as possible after blood collection and stored at -20°C until analysis. Since the trial was performed according to general clinical practice as much as possible, sample collection was not restricted to fasting conditions. The concentrations of 20 serum protein biomarkers for disease activity (SAA1, IL6, TNFR1, VEGFA, PYD, MMP1, ICAM1, Calprotectin, YKL40, MMP3, EGF, IL1RA, VCAM1, Leptin, Resistin, CRP, IL8, CCL22, IL1B, and IL6R) were

measured by customized immunoassays (Sector Imager 6000 (Meso Scale Discovery, Gaithersburg, Maryland) or individual enzyme-linked immunosorbent assays). The reagents used were designed to block interference from rheumatoid factor and other heterophilic antibodies.[14]

**Multi-biomarker disease activity (MBDA) score algorithm**

A disease activity algorithm using a pre-specified formula including 12 of the 20 aforementioned biomarkers was applied to calculate MBDA scores in RA patients from CAMERA (see Figure 1). This algorithm used serum biomarker concentrations to separately estimate the TJC28, SJC28, and VAS-GH. The estimates for TJC28, SJC28, and VAS-GH were combined with a CRP test result to calculate an overall MBDA score, an integer ranging from 1 to 100, using a formula analogous to that of the DAS28 (see Figure 1). The algorithm of the MBDA score was previously developed and trained in other data using independent serum samples from the Index for Rheumatoid Arthritis Measurement (InForm, n=512) and Brigham and Women's Rheumatoid Arthritis Sequential Study (BRASS, n=167) observational cohort studies.[19, 20] MBDA score thresholds were defined by calculating the MBDA score values equivalent to established DAS28-CRP thresholds separating low, moderate and high disease activity.[21] The resulting thresholds defined MBDA score as <30 for low, in between 30-44 for moderate, and >44 for high disease activity.

$$\text{MBDA score} = (0.56*\sqrt{\text{IPTJC}} + 0.28*\sqrt{\text{IPSJC}} + 0.14*\text{IPVAS} + 0.36*\log(\text{CRP}+1) + 0.96) *10.53 + 1$$

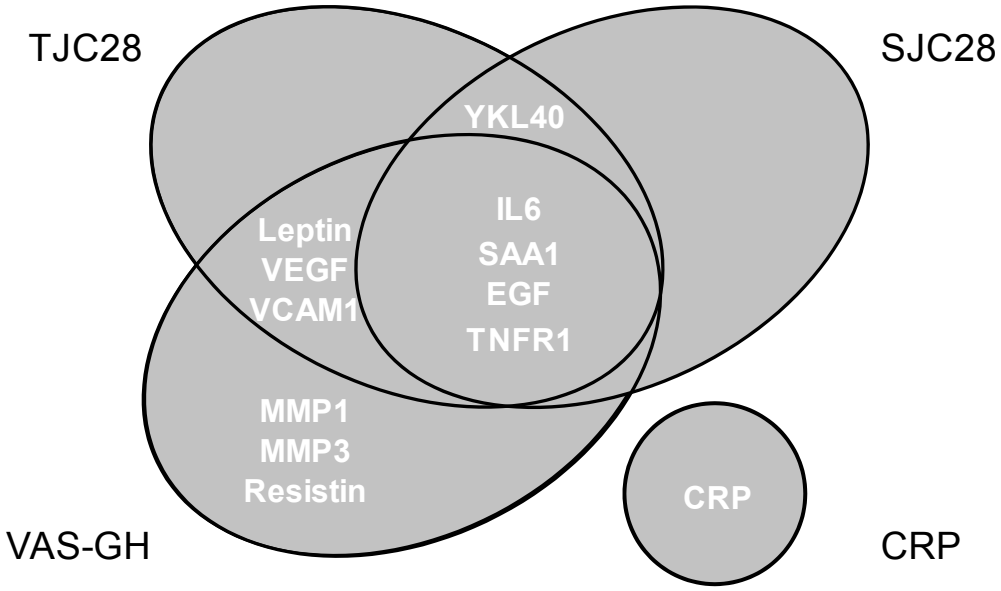



**Figure 1.** The MBDA score algorithm uses the same equation as the DAS28-CRP, with biomarkers used to predict the swollen joint count (SJC28), tender joint count (TJC28), and visual analogue scale of general well-being (VAS-GH) components of the equation. The Venn diagram lists the MBDA score biomarkers used to predict each MBDA score component. This algorithm provides a MBDA score between 1 and 100.
IPTJC= predicted tender joint count; IPSJC= predicted swollen joint count; IPVAS= predicted visual analogue scale of general well-being.

**Statistical analysis**

The associations between individual biomarkers concentrations (log-transformed) and disease activity (DAS28, DAS28-CRP, SJC28, TJC28 and VAS-GH) were assessed by Pearson correlation (r). P values for correlations were calculated by permutation testing and adjusted for multiple hypothesis testing by calculating q values by the false discovery rate (FDR) method of Benjamini and Hochberg.[22]

The performance of the MBDA score algorithm was evaluated by the Pearson correlation (r) between MBDA scores (total score and separate components) and the clinical disease activity (DAS28-CRP, DAS28, and individual components). Further, the discriminative value between patients with moderate/high disease activity and those with low disease activity at the baseline and 6 months visits was tested using the area under the receiver operating characteristic curve (AUROC). The reference classification for the ROC analysis was based on a DAS28-CRP cut off of 2.67, which is the threshold separating low disease activity from moderate and high disease activity.[21]

Further the agreement between the classification of disease activity (low, moderate and high disease activity) according to the MBDA score and DAS28-CRP respectively DAS28 was calculated using (weighted) Kappa.

To ensure that performance was not overestimated due to the inclusion of two samples for some patients and samples at baseline and at 6 months (on treatment), subanalyses of samples from baseline and samples on six months was performed.

To investigate whether the MBDA score has (additional) prognostic value for progression of radiographic joint damage over 2 years, logistic regression analysis was used. Univariate logistic regression analysis was performed with the MBDA score as independent variable and progression in SharpvanderHeijde score (SHS) over two years (progression >0 SHS units) as dependent variable. This analysis was compared with an analysis with the DAS28-CRP as independent variable in the same patient population. Multivariate (logistic) analyses with other well known prognostics factors for progression of joint damage (rheumatoid factor (RF) and baseline joint damage) were also performed (with treatment strategy, age, and gender as covariates) to investigate the additional prognostic value of the MBDA score and DAS28-CRP. Separate analyses were performed for the MBDA score and DAS28(CRP) at baseline and at six months.

The statistical software packages R and SPSS15.0 were used for analyses of data. Except where otherwise noticed, a p value $<0.05$ was considered to be statistically significant.

**RESULTS**

Of the 20 proteins examined, 14 were statistically significantly correlated with DAS28-CRP, 11 with DAS28, 11 with swollen joint count, 9 with tender joint count, and 6 with VAS-GH (with a FDR<0.05). Pearson correlations between the individual biomarkers and disease activity measures are presented in Table 1.

| Biomarker | DAS28-CRP R | DAS28-CRP q | DAS28 R | DAS28 q | SJC R | SJC q | TJC R | TJC q | VAS-GH R | VAS-GH q |
|---|---|---|---|---|---|---|---|---|---|---|
| Calprotectin | **0.56** | **<0.01** | **0.49** | **<0.01** | **0.38** | **<0.01** | **0.33** | **<0.01** | **0.25** | **<0.01** |
| YKL40 | **0.42** | **<0.01** | **0.34** | **<0.01** | **0.35** | **<0.01** | **0.30** | **<0.01** | 0.15 | 0.18 |
| CCL22 | -0.04 | 0.75 | -0.02 | 0.90 | -0.13 | 0.19 | -0.03 | 0.73 | 0.01 | 0.94 |
| CRP | **0.69** | **<0.01** | **0.58** | **<0.01** | **0.41** | **<0.01** | **0.36** | **<0.01** | **0.32** | **<0.01** |
| EGF | -0.07 | 0.46 | -0.06 | 0.77 | -0.08 | 0.42 | -0.12 | 0.28 | 0.02 | 0.94 |
| ICAM1 | **0.23** | **0.02** | **0.21** | **0.02** | 0.13 | 0.20 | 0.08 | 0.44 | 0.09 | 0.48 |
| IL1β | **0.45** | **<0.01** | **0.36** | **<0.01** | **0.34** | **<0.01** | **0.31** | **<0.01** | **0.27** | **0.03** |
| IL6 | **0.69** | **<0.01** | **0.66** | **<0.01** | **0.50** | **<0.01** | **0.41** | **<0.01** | **0.43** | **<0.01** |
| IL6R | 0.01 | 0.97 | 0.04 | 0.77 | 0.03 | 0.71 | 0.02 | 0.89 | 0.08 | 0.53 |
| IL8 | **0.47** | **<0.01** | **0.43** | **<0.01** | **0.46** | **<0.01** | **0.30** | **<0.01** | **0.23** | **0.03** |
| IL1RA | 0.01 | 0.97 | -0.02 | 0.79 | 0.05 | 0.58 | -0.09 | 0.44 | -0.03 | 0.94 |
| Leptin | 0.00 | 0.97 | 0.08 | 0.58 | -0.07 | 0.53 | -0.06 | 0.56 | 0.16 | 0.18 |
| MMP1 | **0.36** | **<0.01** | **0.31** | **<0.01** | **0.29** | **<0.01** | 0.19 | 0.06 | **0.21** | 0.05 |
| MMP3 | **0.51** | **<0.01** | **0.49** | **<0.01** | **0.40** | **<0.01** | **0.28** | **<0.01** | **0.26** | 0.05 |
| Pyridinoline | **0.23** | **0.04** | 0.12 | 0.34 | **0.29** | **<0.01** | 0.26 | 0.09 | 0.12 | 0.39 |
| Resistin | **0.22** | **0.03** | 0.17 | 0.08 | 0.13 | 0.20 | 0.13 | 0.28 | 0.10 | 0.43 |
| SAA1 | **0.66** | **<0.01** | **0.57** | **<0.01** | **0.43** | **<0.01** | **0.37** | **<0.01** | **0.32** | **<0.01** |
| TNFR1 | **0.36** | **<0.01** | **0.28** | **<0.01** | **0.30** | **<0.01** | **0.24** | **0.02** | 0.13 | 0.30 |
| VCAM1 | 0.13 | 0.24 | 0.08 | 0.58 | 0.14 | 0.20 | 0.08 | 0.56 | -0.03 | 0.79 |
| VEGFA | **0.29** | **<0.01** | **0.26** | 0.05 | 0.18 | 0.12 | 0.07 | 0.56 | 0.14 | 0.18 |

**Table 1** Pearson correlations between individual biomarkers and clinical disease activity measures.
Correlations are shown for all biomarkers with DAS28(CRP) and individual components. Q values reflect the false discovery rate and are calculated by adjusting the p values for multiple hypothesis testing. Statistical significant associations (q<0.05) are shown in bold. DAS28-CRP= disease activity score based on 28 joints with CRP instead of ESR as component; DAS28= original disease activity score based on 28 joints; SJC28= swollen joint count based on 28 joints; TJC28= tender joint count based on 28 joints; VAS-GH= visual analogue scale general well-being.

The MBDA score was calculated using 12 of the 20 biomarkers. Figure 2 illustrates that the MBDA score achieved a statistically significant correlation to the DAS28-CRP (r=0.73; p<0.001) as well a statistically significant AUROC (0.87; p<0.001), distinguishing between low disease activity and moderate/high disease activity. This is also shown for the individual components (cut-off used was median value; Figure 2). The pre-specified ARUOC analysis was conducted using a DAS28-CRP cut off of 2.67. It was noted that more patients had high disease activity than low disease activity using this cut off. To assess the impact of imbalance in the groups of the disease activity levels, the AUROC was also calculated using a cut off that was set equal to the median DAS28-CRP of 4.6. The resulting AUROC was 0.83, similar to the AUROC obtained using the pre-specific cut off of 2.67.
To ensure that performance was not overestimated due to the inclusion of two samples for some patients and samples at two time points, separate subanalyses of samples from baseline and samples from 6 months were performed, in which the algorithm performance was the same from that observed when all samples were included (data not shown).

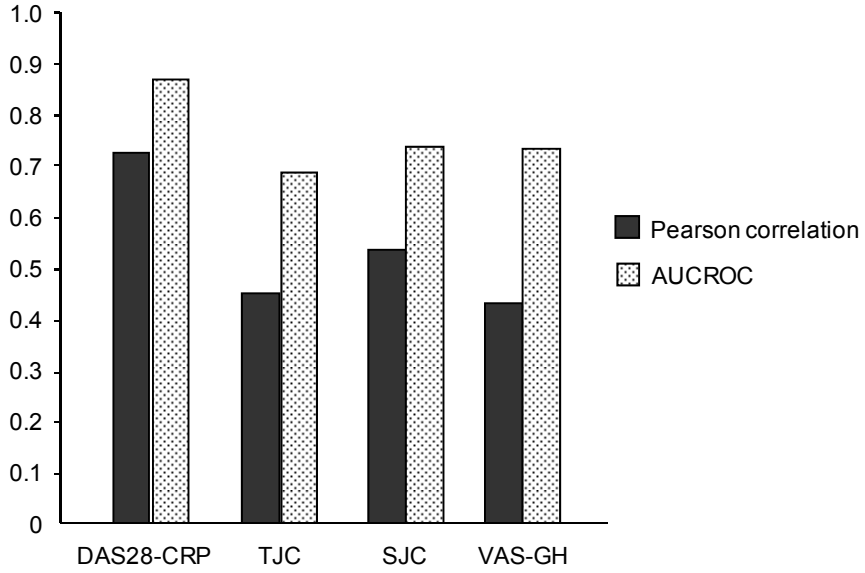



**Figure 2.** Correlations of the MBDA score with the components of the disease activity score (DAS28-CRP).
Pearson correlation are represented in black bars, AUROC curves in dotted bars, distinguishing low from moderate/high disease activity. DAS28-CRP= disease activity score based on 28 joints with CRP instead of ESR as component; TJC= tender joint count based on 28 joints; SJC= swollen joint count based on 28 joints; VAS-GH= visual analogue scale general well-being.

The kappa for the agreement (based on 6 months data) between MBDA score and DAS28-CRP for classification of the disease activity level was 0.32 (95%CI 0.11-0.53, p=0.02), this was 0.29 (95%CI 0.07-0.50, p=0.004) for MBDA score and DAS28; weighted kappa showed values of respectively 0.39 and 0.41 (see Table 2).

| | DAS28-CRP | | | DAS28 | | |
|---|---|---|---|---|---|---|
| **MBDA score** | low | moderate | high | low | moderate | high |
| Low | 9 | 3 | 2 | 10 | 4 | 0 |
| Moderate | 7 | 7 | 4 | 9 | 7 | 2 |
| High | 2 | 4 | 10 | 2 | 6 | 8 |

**Table 2** Agreement between classification of disease activity (low, moderate and high) according to the MBDA score and DAS28-CRP respectively DAS28 based on 6 months values.
Numbers of agreement between the classifications are shown. Low= MBDA score <30, DAS28-CRP <2.7, DAS28 <3.2; moderate= MBDA score ≤44, DAS28-CRP ≤4.1, DAS28 ≤5.1; high= MBDA score >44, DAS28-CRP >4.1, DAS28 >5.1.

Univariate linear regression analysis showed that the MBDA score at baseline was not an independent predictor for radiographic progression (OR=1.018, 95%CI 0.988-1.049, p=0.25) after 2 years of treatment; this also applied for DAS28-CRP (OR=1.041, 95%CI 0.645-1.680, p=0.87).

For 6 months value of the MBDA score this was OR=1.041 (95%CI 0.645-1.680, p=0.87); comparable with the 6 month value for DAS28-CRP (OR=1.121, 95%CI 0.750-1.674, p=0.58).

After inclusion of other known predictors for long-term outcome (RF and baseline damage) in a multivariate logistic regression model the baseline MBDA score was borderline significant as an independent predictor for progression of joint damage (OR=1.033, 95%CI 0.995-1.072, p=0.09) next to RF (OR=1.768, 95%CI 0.396-7.885, p=0.46) and baseline joint damage (OR= 4.213, 95%CI 0.878-20.211, p=0.07). When baseline DAS28-CRP was used in the model instead of the MBDA score this result was less clear (OR=1.155, 95%CI 0.674-1.980, p=0.60) next to RF (OR=2.294, 95%CI 0.534-9.847, p=0.26) and baseline joint damage (OR=3.359, 95%CI 0.732-15.411, p=0.12). When the 6 months values of the MBDA score and DAS28-CRP were used comparable results were seen for the multivariate logistic model (MBDA score at 6 months: OR=1.032, 95%CI 0.982-1.084, p=0.21); this was OR=1.234, 95%CI 0.752-2.024, p=0.41 for the DAS28-CRP at 6 months).

In response to the treatment as used in the CAMERA study (n=46), the mean (SD) MBDA score dropped from 53 (18) at baseline to 39 (16) at the 6 month visit (p<0.0001, Figure 3). The TC and CT treatment strategies were also considered separately, showing a decrease in MBDA score in TC treatment strategy (n=31) from 53 (17) to 35 (14) (p<0.0001). In CT treatment strategy (n=15), the MBDA score decreased from 55 (20) to 46 (19) (p=0.07*).*

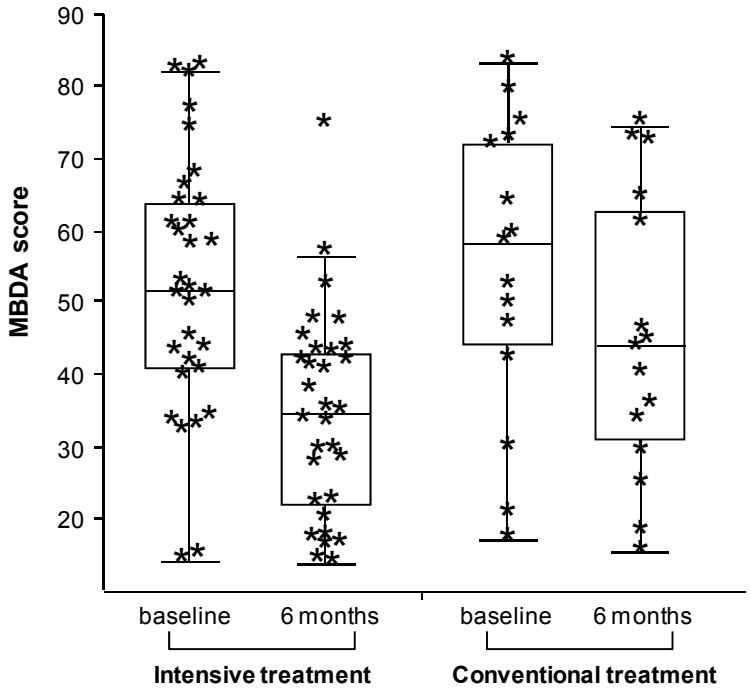



**Figure 3.** The MBDA score by treatment strategy and time point. For each treatment strategy (i.e. intensive tight control MTX-based and conventional MTX-based treatment strategy) the results of the MBDA score are showed at baseline and after 6 months of treatment. Only results of patients with MBDA scores at baseline and months are shown.

## DISCUSSION

Tight control studies such as CAMERA, which include regular assessments of disease activity and intensive treatment approaches, have demonstrated beneficial effects in long-term patient outcomes for RA.[11, 15] A recent meta-analysis of 6 tight control trials in RA reported that patients treated with the tight control strategies had significantly greater DAS28 responses and better clinical outcomes than patients treated according to usual care (weighted mean difference (WMD)=0.59, $p<0.001$).[23]

Although tight control strategies have been integrated into RA treatment guidelines,[7, 8] the current tools available for measuring disease activity might not be easily implemented in clinical practices around the world. A comprehensive panel of relevant serum protein biomarkers, containing biologically rich RA disease activity information, has the potential to assess disease activity in an objective manner and thereby facilitate use of tight control strategies. A multi-biomarkers test may provide new and complementary information which, when used in concert with DAS28 and/or other existing disease activity measures, could enhance disease activity assessments and further improve tight control.

In the present study, 20 serum biomarkers of RA disease activity were evaluated to confirm the performance of the MBDA score, a predefined biomarker-based test for RA disease activity. The individual biomarkers represented a broad range of biological pathways associated with RA disease pathophysiology.[24] Some biomarkers that were found to be individually associated with disease activity in this study are not among the 12 biomarkers included in the MBDA score. This may be because they provide redundant information and are not independently predictive of disease activity in a multivariate model when other biomarkers are present. Conversely, some biomarkers that do not have significant individual correlations with disease activity in the CAMERA study are included in the MBDA score. One reason for that is that a biomarker may provide useful information in combination with other biomarkers but not individually.[25] Also, biomarker results vary between individual cohorts because of differences in patient populations and study designs. To identify robust, reproducible biomarkers, multiple studies are needed. The 12 biomarkers included in the MBDA score algorithm were selected and prioritized on the basis of several feasibility and algorithm development studies in over 1100 patient samples from 3 study groups (InFoRM, BRASS, and Oklahoma Medical Research Foundation (OMRF)), which included patients with a wide spectrum of disease activity.[20] Validation studies of the pre-specified 12-biomarker test have also been carried out in independent sets of RA patients with diverse characteristics (manuscripts in development).

Here, we present data on MBDA score performance, using a patient population from the CAMERA study. Results from the CAMERA study had previously shown that intensive treatment, driven by regular clinical assessment of disease activity aiming at remission, could improve patient outcomes in early RA. The final MBDA score algorithm, which combines information from 12 biomarkers, performed well when evaluated in CAMERA; a high MBDA score was associated with high disease activity scores (DAS28-CRP and

DAS28) while a low MBDA score was associated with low disease activity both at baseline and after 6 months of treatment. MBDA scores were also highly correlated with clinical measures of disease activity (DAS28(-CRP) and its components). Kappa values also showed that there is fair agreement between disease activity levels according to both measures, although it is important to realize that there is no true gold standard for disease activity. Estimates of the correlation and AUROC might be influenced by the characteristics of a given cohort and may vary in future studies.

In this analysis, neither the MBDA score nor other clinical were clearly predictive of radiographic progression. This could be because the study population had quite limited progression over the 2 years examined, or because of the limited sample size. Additional studies will further clarify the predictive value of the MBDA score for future radiographic progression.

To determine if MBDA scores at baseline and 6 months were affected by different RA management strategies, changes in MBDA scores were examined in patients receiving TC and CT strategy (Figure 3). MBDA scores improved in response to treatment with a 15-point decrease across all 46 patients; a significant decrease was observed in the TC strategy. While obtained from a small patient population, these results suggest that monitoring of disease activity with the MBDA score can identify changes in disease activity and response to treatment, leading to improved patient outcomes in a similar manner to the clinical disease activity index (DAS28).

Although biomarkers could not be assessed in all patients from the CAMERA study the populations characteristics (i.e. demographics and clinical variables) in the subset of patients in which biomarkers were assessed in general did not differ from the total CAMERA population (only small differences in numbers of TJC and SJC were seen) and the treatment effect as assessed using the DAS28 was also similar to the effect in the total population.

Through monitoring RA disease activity and tailoring treatment strategies specifically to an individual patient's needs, low disease activity and possibly remission is attainable. Serum protein biomarkers representing a variety of biological pathways are consistently associated with RA disease activity in different patient cohorts and might therefore be suitable candidates for monitoring disease activity.

The study results also suggest that the MBDA score has the potential to track disease activity over time in patients with RA who are on drug therapy although this should be explored in longer term follow-up. For this purpose, more measurements over time should be evaluated and ultimately a trial evaluating the effect of a tight control strategy using the MBDA score (as compared to a clinical disease activity score) should be performed.

In conclusion, the MBDA score performed well at assessing (and tracking) disease activity in RA patients in the CAMERA study. This score could be used in conjunction with a physical examination to quantify overall disease activity in a patient management plan. Changes in response to treatment could be observed using the MBDA score, although longer term investigations are needed.

## REFERENCES


1. Kvien TK. Epidemiology and burden of illness of rheumatoid arthritis. Pharmacoeconomics 2004;22 Suppl 1:1-12.
2. Maini R, St Clair EW, Breedveld F, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet 1999;354:1932-9.
3. Isaacs JD. Therapeutic agents for patients with rheumatoid arthritis and an inadequate response to tumour necrosis factor-alpha antagonists. Expert Opin Biol Ther 2009;9:1463-75.
4. Feely MG, Erickson A, O'Dell JR. Therapeutic options for rheumatoid arthritis. Expert Opin Pharmacother 2009;10:2095-106.
5. Boers M. Understanding the window of opportunity concept in early rheumatoid arthritis. Arthritis Rheum 2003;48:1771-4.
6. Atar D, Birkeland KI, Uhlig T. 'Treat to target': moving targets from hypertension, hyperlipidaemia and diabetes to rheumatoid arthritis. Ann Rheum Dis 2010;69:629-30.
7. Kiely PD, Brown AK, Edwards CJ, et al. Contemporary treatment principles for early rheumatoid arthritis: a consensus statement. Rheumatology (Oxford) 2009;48:765-72.
8. Smolen JS, Aletaha D, Bijlsma JW, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis 2010;69:631-7.
9. Bakker MF, Jacobs JW, Verstappen SM, et al. Tight control in the treatment of rheumatoid arthritis: efficacy and feasibility. Ann Rheum Dis 2007;66 Suppl 3:iii56-60.
10. Bakker MF, Jacobs JWG, Welsing PMJ, et al. Are switches from oral to subcutaneous MTX or addition of cyclosporine to MTX useful steps in a tight control treatment strategy for RA? A post-hoc analysis of the CAMERA study. Ann Rheum Dis 2010;69:1849-52.
11. Verstappen SM, Jacobs JW, van der Veen MJ, et al. Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open label trial). Ann Rheum Dis 2007;66:1443-9.
12. Shen Y, Knowlton N, Turner M, et al. Stepwise discovery of disease activity biomarkers in rheumatoid arthritis. EULAR 2010;THU0066.
13. Eastman S, Manning W, Qureshi F, et al. Assay development for precise measurement of disease activity serum biomarkers. EULAR 2010;THU0065.
14. Nam J, Villeneuve E, Emery P. The role of biomarkers in the management of patients with rheumatoid arthritis. Curr Rheumatol Rep 2009;11:371-7.
15. Verstappen SM, Bakker MF, Heurkens AH, et al. Adverse events and factors associated with toxicity in patients with early rheumatoid arthritis treated with methotrexate tight control therapy (the CAMERA study). Ann Rheum Dis 2010;69:1044-8.
16. 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.
17. Prevoo ML, van 't Hof MA, Kuper HH, et al. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38:44-8.
18. Bijlsma JWJ, Oude Heuvel CH, Zaalberg A. Development and validation of the Dutch questionnaire capacities of daily life (VDF) for patients with rheumatoid arthritis. J Rehabil Sci 1990;3:71-4.
19. Cavet G, Centola M, Shen Y, et al. Development of a multi-biomarker test for rheumatoid arthritis disease activity, on behalf of the InFoRM and BRASS study groups. EULAR 2010;OP278.
20. Fleischmann RM, Curtis JR, Hamburger M, et al. Rheumatoid arthritis population characteristics in InFoRM, a longitudinal observational study, on behalf of the InFoRM study group. EULAR 2010;SAT0518.
21. Inoue E, Yamanaka H, Hara M, et al. Comparison of Disease Activity Score (DAS)28- erythrocyte sedimentation rate and DAS28- C-reactive protein threshold values. Ann Rheum Dis 2007;66:407-9.
22. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc Series B Stat Methodol 1995;57:289-300.

23. Schipper LG, van Hulst LT, Grol R, et al. Meta-analysis of tight control strategies in rheumatoid arthritis: protocolized treatment has additional value with respect to the clinical outcome. Rheumatology (Oxford) 2010;49:2154-64.
24. Ramanujan S, Centola M, Cavet G, et al. Multi-protein biomarker panel integrates critical pathophysiologic mechanisms in measurement of RA disease activity. EULAR 2010;FRI0034.
25. Afifi AA, Clark V, May S. Chapter 7. In: Computer-aided multivariate analysis, 4th edition. Texts in statistical science; Chapman&Hall/CRC 2004.

# SUMMARY & DISCUSSION

Chapter 12

## SUMMARY

Treating patients with rheumatoid arthritis (RA) has changed the past decades with great steps forward in the use of treatment strategies as well as changes in setting the aim of treatment. Research has been done evaluating strategies to reach the aim of remission or low disease activity instead of clinically relevant improvement. These strategies can be grouped as 'tight control', which is evaluated in this thesis. Tight control can be defined as a treatment strategy with dose and strategy adjustments tailored to the disease activity of each individual RA patient aimed at a predefined level (i.e. 'treat to target') of low disease activity or preferably remission within a reasonable period of time. In the first part of this thesis aspects of tight control are described, including effectiveness, adverse effects, and long-term outcome. In the second part, research into possible predictors of RA to prevent under- and overtreatment of the individual RA patient is described.

The first question addressed in the first part of this thesis dedicated to the tight control principle was: *can tight control be considered as an efficacious and feasible principle in the treatment of RA patients?* To evaluate these aspects four randomized controlled trials (i.e. FIN-RACo, TICORA, BeSt, and CAMERA) in patients with early RA were reviewed (**chapter 2**). The evaluated trials showed that the range of remission rates in the tight control groups (50 - 68%) was significantly better than that in the comparison groups (16 - 41%). From this it can be concluded that tight control is a promising new treatment principle for clinical trials and probably daily practice.

With the introduction of tight control, more intensive treatment strategies were used in the treatment of early RA patients, compared to formerly used strategies. This could lead to more adverse events (AEs). This topic was investigated in the CAMERA study and described in **chapter 3**. The research question was: *is the occurrence of AEs different in patients with early RA who were treated with methotrexate (MTX) according to an intensive treatment strategy compared to a conventional treatment strategy?* Results showed that, although more patients experienced possible MTX related AEs in the intensive treatment strategy compared to the conventional treatment strategy, the severity of AEs was relatively mild. Most AEs were reversible in both groups. The clinical benefit in the intensive treatment strategy of CAMERA was evidently higher compared to that of the conventional strategy and outweighs the slightly higher risk of AEs. This supports the use of intensive MTX-based treatment as first (in case of step-up therapy) or anchor DMARD (in case of combination therapy) in early RA in daily practice. However, when starting MTX in patients with early RA, attention should be given to a high BMI, increased levels of serum liver enzymes, and decreased renal function; these factors showed to be related with MTX withdrawal due to AEs.

With tight control, different (types of) medications can be used in the treatment strategy to reach the aim of remission. In **chapter 4** the question was addressed whether *the subcutaneous MTX (scMTX) strategy step and cyclosporine strategy step, used as next steps within the tight control treatment strategy of the CAMERA trial after reaching the maximum (tolerable) oral MTX dose, were effective steps in case remission was not yet present*. The results showed that the scMTX strategy step is a useful step after oral MTX in a tight control strategy in early RA whereas the following cyclosporine step seems ineffective. Therefore, if oral MTX has insufficient effect, it can be recommended to use scMTX as next step in a tight control strategy, whereas addition of cyclosporine is not recommended.

Based on the research depicted in previous chapters of this thesis, tight control is a good treatment strategy on the short-term. To evaluate the longer term effectiveness of this strategy the next questions were investigated: *what are the long-term effects of a 2-year MTX-based tight control treatment strategy compared to conventional MTX-based treatment strategy and is an early response to treatment of (added) predictive value for long-term (5 year) outcome of patients with respect to disease activity and progression of radiographic joint damage?* The results of these analyses were addressed in **chapter 5**. After 5 years of treatment, differences at 2 years (the end of the CAMERA trial) regarding disease activity and progression of joint damage between the treatment strategy groups were not evident anymore. A possible explanation is that the tight control principle was maintained less strictly after the end of the trial. An early good-response (determined at 6 months) to treatment proved to be an independent predictor of better 5 years outcome, irrespective of the treatment strategy used. These data suggest to continue use of the tight control principle over time and to use more adequate treatment strategy steps early in the disease in inadequate responders.

The tight control studies performed show good results, but still there is room for improvement, regarding the number of patients in remission and the long-term outcome. As an extension of the tight control strategy as investigated in the CAMERA study it was investigated: *is combining prednisone with a MTX-based tight control strategy from start of treatment of early RA more effective than applying this strategy without prednisone regarding both disease activity and outcome, i.e. erosive joint damage?* This study (**chapter 6**) showed that low-dose prednisone indeed increased both effectiveness and outcome without increasing toxicity over 2 years, when added to the tight control MTX-based treatment strategy. Patients in the tight control MTX-based strategy with low-dose prednisone reached in an earlier phase of the disease sustained remission and fewer patients needed biological treatment compared to the MTX-based strategy group without low-dose prednisone. These results show that the need for (early) treatment with biologicals is decreased, which is an important finding in the current discussions on costs in health care.

*Overall, this first part of the thesis shows that tight control is effective, especially in case of adding low-dose prednisone to a MTX-based tight control strategy. Relatively mild adverse events were observed. As treatment strategy step, switching from oral to subcutaneous MTX seems to be effective, in contrast to adding cyclosporine to MTX. Tight control as treatment strategy probably needs to be continued also on the longer term.*

The second part of the thesis deals with prediction of outcome of RA. The first item that was addressed was whether the MTX dose needed in an individual patient to obtain an optimal response can be predicted. To this aim, disease activity assessments over time in relation to increases in MTX dose were analysed. This was described in **chapter 7**, answering the question: *can the most optimal MTX dose in individual patients and the level of disease activity reached at this dose be predicted?* Results showed that although the optimally effective dose can be determined in individual RA patients, the predictive value is low. The study suggested that a starting dose of MTX of at least 15 mg/wk seems a good initial choice. With frequently monitoring of disease activity over time with stepping up MTX therapy, it can be determined whether further improvement in disease activity can be expected and whether the strategy has to be expanded.

In tight control strategies, frequent monitoring of the disease activity is an important concept to reach the aim of low disease activity or remission of RA and thereby to prevent further radiographic joint damage. This monitoring is mostly done with disease activity indices, the disease activity score based on 28 joints (DAS28) being one of the most used instruments. However, the ability of this instrument to predict outcome (i.e. joint destruction) in the individual patient is not yet clear. Therefore DAS28 as a tight control prediction instrument was evaluated in this thesis. Research addressing the question *what is the influence of tender points (TP) in patients with RA on the disease activity index DAS28?* was described in **chapter 8**. Clearly DAS28 is influenced by coexistence of TP in RA patients, due to the strong association of TP count with the less objective DAS28 components VAS general well-being and tender joint count. When applying DAS28-guided individual treatment strategies, a full clinical evaluation of the patient is still required. Additionally, factors such as non-inflammatory generalized pain and TP should be evaluated, because of their influence on DAS28 and with that, the therapeutic approach.

In RA patients, the pattern of involved joints may differ. Using DAS28 (that excludes joints of feet) as monitoring instrument, it is also important to know to what extent this instrument is useful for the prediction of outcome of different subgroups of RA patients. The question addressed in **chapter 9** was: *does a subgroup of patients exist, especially early in the disease, with a dominant involvement of the feet and does this have consequences for the relation of disease activity measured with long-term outcome?* The analysis showed that in the subgroup of RA patients with predominantly foot problems, DAS28 underestimated the disease activity and the expected joint damage. This was especially the case during the first

2 years of the disease. For tight control strategies particularly, it could be a problem, using DAS28 (or another disease activity index not including the feet) as monitoring instrument and remission or low disease activity definition as target. For follow-up of individual patients, assessment of all frequently in RA involved joints seems indicated, especially early in the disease course.

So far prediction of the outcome of RA in this thesis was investigated using clinical variables. Next to clinical variables other predictors, like biomarkers, could be used in predicting the (long-term) outcome. Research addressing this topic is described in the last part of this thesis. The first question was addressed in **chapter 10**: *can the long-term radiographic and clinical outcome in patients with early RA be predicted by investigating biomarkers of bone and cartilage (C2C, C1,2C, CS846, and CPII) determined early in the disease?* Results indicated that some of these biomarkers have a small predictive value for long-term outcome in early RA, but clearly less compared to established clinical predictors. Only changes in C1,2C and CPII in the first year after disease onset predicted respectively radiographic progression and disease activity over 5 years, though the predictive value was too small to be useful in daily clinical practice.

Combination sets of biomarkers, also including those not associated with bone and cartilage, might be better predictors when compared to the single biomarkers of bone and cartilage as described above. To evaluate this hypothesis, for the final chapter of this thesis (**chapter 11**), the question was posed: *are values of a broad set of serum biomarkers related to RA disease activity, and what is the performance of a disease activity algorithm (MBDA score) of biomarkers in an independent patient population?* Results showed that the algorithm score has a high cross-sectional correlation and fair level of agreement with DAS28; the score can classify patients with low disease activity. Although the MBDA score performed well, longitudinal validation is still needed to confirm whether this algorithm can be used to guide appropriate treatment strategies in individual RA patients.

*Overall, from this second part of the thesis on (long-term) prediction, it can be concluded that the use of DAS28 as a monitoring instrument for the individual patient is not always straightforward. The presence of tender points influences the disease activity state as calculated by the DAS28 and the use of this index for tight control can lead to undertreatment of RA patients with predominantly foot involvement. Prediction of the most optimal individual dose of MTX with clinical variables and prediction of disease activity and radiographic outcome with biomarkers was explored, but still needs further research.*

## DISCUSSION

Rheumatoid arthritis (RA) is a chronic disease with potentially severe manifestations, complications and outcome. The ultimate goal of treatment is to cure the disease. However, as long as this is not possible with the available treatment options, sustained remission and the absence of joint damage is the current goal of treatment.[1-4]
To reach this goal, increasingly treatment strategies according 'tight control' and 'treat to target' principles are being applied. This thesis shows that tight control is effective and feasible in early RA patients. The second Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA-II) study shows that a tight control strategy starting with cheap drugs is very effective; the radiographic results of this trial clearly support the existence of a 'window of opportunity' in early RA. Weighing efficacy and toxicity in CAMERA-II, efficacy clearly outweighs toxicity, as was also shown in the first CAMERA study.
With several different treatment strategies tight control can be applied, but there is always room for improvement and fine-tuning. For instance in determining which strategy steps are useful. Subsequent treatment strategy steps should always be evidence-based, like the subcutaneous MTX strategy step investigated in this thesis. Also, it is important to decide at which moment early in the treatment of RA, medication should be added to the strategy. This decision can be based upon the response to treatment after 6 months after start of treatment, as demonstrated in this thesis, and possibly even earlier, already after 3 months. Using the "window of opportunity" optimally to suppress the disease, the long-term outcome of RA is better, and less intensive therapy is needed.[9, 10] If higher starting doses of the anchor drug MTX are used, like 15 mg/wk MTX found in our research, already at 3 months the early response to treatment can be determined. Tight control with the treat to target principle, preferentially remission, should be continued on the longer term. This requires frequently monitoring (i.e. monthly) in patients with high or moderate disease activity and less frequently (every 3 to 6 months) in patients with sustained low disease activity or remission.[9] This thesis shows that patients could be treated adequately in a tight control strategy starting with 15 mg/wk MTX in combination with 10 mg/day prednisone.[1, 11-14] In case of inadequate response to treatment after 3 to 6 months, a biological could be added. We have no data on continuing the prednisone for shorter or longer than 2 years in combination with a MTX-based tight controlled strategy in early RA; this should be further investigated.

For treating to target, assessment of the target, e.g. remission should be valid. Currently, the disease activity score based on 28 joints (DAS28), the clinical disease activity index (CDAI), and simplified disease activity index (SDAI) are the most frequently used disease activity indices.[15, 16] However, this thesis shows that these indices are not optimal for 'tight control' and 'treat to target' principles and might lead to underestimation of the actual disease activity.[17-21] The reason is that in these indices joints of feet are not included.

Other studies showed that these indices lack accuracy for remission.[25, 26] A further drawback of these indices is that they (especially DAS28) might be influenced by presence of tender points, shown in this thesis and by erythrocyte sedimentation rate, age, and gender as was found by others, which distorts estimation of the actual disease activity.[22-24] These drawbacks are the reason that none of them was used for the computer assisted tight control strategy in CAMERA and CAMERA-II.
A suggestion for optimizing these indices would be to include any frequently in RA involved joint, including those of the feet. Until the perfect solution has been found, disease activity states as assessed with these indices should be interpreted with caution, especially low or remission disease activity states. To check these states, regularly joints (also of feet) and radiographs of hands and feet should be assessed. Another important aspect is to improve the current remission criteria. Very recently, new (ACR/EULAR) definitions of remission for clinical trials have been developed which are primarily based on SDAI and CDAI indices. However, they still do not take the joints of feet into account.[27]

Optimal choices regarding tight control strategies would be aided if there were additional predictors of the outcome of each individual RA patient, next to the already known predictors. Predicting the individual MTX dose needed for an optimal response as described in this thesis is important, but these preliminary results need to be further evaluated. Another possibility is looking at prediction of outcome by biomarkers. Our study and those of others show that individual biomarkers still are not able to reliably predict the long-term outcome in individual patients with early RA, although some have a relation with radiographic progression and/or disease activity.[28-38] A promising option might be using a set of different biomarkers, e.g. the MBDA score described in this thesis, assessing disease activity in an objective manner without the need for joint counts and visual analogue scales. However, this use of biomarkers as predictor in clinical practice also needs to be further investigated. Prediction of treatment efficacy is the main goal of the Dutch Centre for Translational Molecular Medicine study on RA, called TRACER. Six university departments of rheumatology work together with small and medium sized industries and large pharmaceutical companies to develop prediction tools and treatment rules. This collaboration might lead to future breakthroughs in this concept.
In all, the options for patients with RA clearly have improved the past years, thanks to research like described in this thesis. Research is and should be an ongoing process until RA can be cured.

## REFERENCES


1. Combe B, Landewe R, Lukas C, et al. EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2007;66:34-45.
2. Mierau M, Schoels M, Gonda G, et al. Assessing remission in clinical practice. Rheumatology (Oxford) 2007;46:975-9.
3. Smolen JS, Aletaha D. What should be our treatment goal in rheumatoid arthritis today? Clin Exp Rheumatol 2006;24:S007-S13.
4. Molenaar ET, Voskuyl AE, Dinant HJ, et al. Progression of radiologic damage in patients with rheumatoid arthritis in clinical remission. Arthritis Rheum 2004;50:36-42.
5. Hoekstra M, Haagsma C, Neef C, et al. Bioavailability of higher dose methotrexate comparing oral and subcutaneous administration in patients with rheumatoid arthritis. J Rheumatol 2004;31:645-8.
6. Fuchs VR. How to think about future health care spending. N Engl J Med 2010;362:965-7.
7. Michaud K, Messer J, Choi HK, et al. Direct medical costs and their predictors in patients with rheumatoid arthritis: a three-year study of 7,527 patients. Arthritis Rheum 2003;48:2750-62.
8. Schoels M, Wong J, Scott DL, et al. Economic aspects of treatment options in rheumatoid arthritis: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis 2010;69:995-1003.
9. Smolen JS, Aletaha D, Bijlsma JW, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis 2010;69:631-7.
10. Smolen JS, Landewe R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis 2010;69:964-75.
11. Knevel R, Schoels M, Huizinga TW, et al. Current evidence for a strategic approach to the management of rheumatoid arthritis with disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis 2010;69:987-94.
12. 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.
13. Gaujoux-Viala C, Smolen JS, Landewe R, et al. Current evidence for the management of rheumatoid arthritis with synthetic disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis 2010;69:1004-9.
14. Nam JL, Winthrop KL, van Vollenhoven RF, et al. Current evidence for the management of rheumatoid arthritis with biological disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of RA. Ann Rheum Dis 2010;69:976-86.
15. Aletaha D, Smolen JS. The Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI) to monitor patients in standard clinical care. Best Pract Res Clin Rheumatol 2007;21:663-75.
16. Prevoo ML, van 't Hof MA, Kuper HH, et al. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38:44-8.
17. Fiehn C, Kessler S, Drexler W, et al. Patients with active rheumatoid arthritis but only few tender and swollen joints: a subgroup with impaired short term outcome. Rheumatol Int 2009;29:655-61.
18. Bakker MF, Jacobs JW, Verstappen SM, et al. Tight control in the treatment of rheumatoid arthritis: efficacy and feasibility. Ann Rheum Dis 2007;66 Suppl 3:iii56-60.
19. Landewe R, van der Heijde D, van der Linden S, et al. Twenty-eight-joint counts invalidate the DAS28 remission definition owing to the omission of the lower extremity joints: a comparison with the original DAS remission. Ann Rheum Dis 2006;65:637-41.
20. van der Heijde DM, Jacobs JW. The original "DAS" and the "DAS28" are not interchangeable: comment on the articles by Prevoo et al. Arthritis Rheum 1998;41:942-5.

21. Schipper LG, van Hulst LT, Grol R, et al. Meta-analysis of tight control strategies in rheumatoid arthritis: protocolized treatment has additional value with respect to the clinical outcome. Rheumatology (Oxford) 2010;49:2154-64.
22. Radovits BJ, Fransen J, van Riel PL, et al. Influence of age and gender on the Disease Activity Score-28 (DAS28) in Rheumatoid Arthritis. Ann Rheum Dis 2007;67:1127-31.
23. Leeb BF, Haindl PM, Maktari A, et al. Disease Activity Score-28 values differ considerably depending on patient's pain perception and sex. J Rheumatol 2007;34:2382-7.
24. Makinen H, Hannonen P, Sokka T. Sex: a major predictor of remission as measured by 28-joint Disease Activity Score (DAS28) in early rheumatoid arthritis? Ann Rheum Dis 2008;67:1052-3.
25. van der Leeden M, Steultjens MP, van Schaardenburg D, et al. Forefoot disease activity in rheumatoid arthritis patients in remission: results of a cohort study. Arthritis Res Ther 2010;12:R3.
26. Makinen H, Kautiainen H, Hannonen P, et al. Is DAS28 an appropriate tool to assess remission in rheumatoid arthritis? Ann Rheum Dis 2005;64:1410-3.
27. Felson DF, Smolen JS, Wells G, et al. American College of Rheumatology/European League against Rheumatism preliminary definition of remission in rheumatoid arthritis for clinical trials. Arthritis And Rheumatism 2010;in press.
28. Hashimoto J, Garnero P, van der Heijde D, et al. A combination of biochemical markers of cartilage and bone turnover, radiographic damage and body mass index to predict the progression of joint destruction in patients with rheumatoid arthritis treated with disease-modifying anti-rheumatic drugs. Mod Rheumatol 2009;19:273-82.
29. Landewe RB, Geusens P, van der Heijde DM, et al. Arthritis instantaneously causes collagen type I and type II degradation in patients with early rheumatoid arthritis: a longitudinal analysis. Ann Rheum Dis 2006;65:40-4.
30. Marotte H, Gineyts E, Miossec P, et al. Effects of infliximab therapy on biological markers of synovium activity and cartilage breakdown in patients with rheumatoid arthritis. Ann Rheum Dis 2009;68:1197-200.
31. Syversen SW, Haavardsholm EA, Boyesen P, et al. Biomarkers in early rheumatoid arthritis: longitudinal associations with inflammation and joint destruction measured by magnetic resonance imaging and conventional radiographs. Ann Rheum Dis 2010;69:845-50.
32. Young-Min S, Cawston T, Marshall N, et al. Biomarkers predict radiographic progression in early rheumatoid arthritis and perform well compared with traditional markers. Arthritis Rheum 2007;56:3236-47.
33. Presentations at the annual meeting of The Finnish Society for Rheumatology, Kuopio, 26-27 January 2006. Scandinavian journal of rheumatology 2006.
34. Visvanathan S, Marini JC, Smolen JS, et al. Changes in biomarkers of inflammation and bone turnover and associations with clinical efficacy following infliximab plus methotrexate therapy in patients with early rheumatoid arthritis. J Rheumatol 2007;34:1465-74.
35. Lindqvist E, Eberhardt K, Bendtzen K, et al. Prognostic laboratory markers of joint damage in rheumatoid arthritis. Ann Rheum Dis 2005;64:196-201.
36. Hammer HB, Odegard S, Syversen SW, et al. Calprotectin (a major S100 leukocyte protein) predicts 10-year radiographic progression in patients with rheumatoid arthritis. Ann Rheum Dis 2010;69:150-4.
37. Gonzalez-Alvaro I, Ortiz AM, Tomero EG, et al. Baseline serum RANKL levels may serve to predict remission in rheumatoid arthritis patients treated with TNF antagonists. Ann Rheum Dis 2007;66:1675-8.
38. Knudsen LS, Klarlund M, Skjodt H, et al. Biomarkers of inflammation in patients with unclassified polyarthritis and early rheumatoid arthritis. relationship to disease activity and radiographic outcome. J Rheumatol 2008;35:1277-87.

# DISEASE ACTIVITY SCORE - DAS28

Appendix

**DAS28 - disease activity score**

The DAS28 is a disease activity score based on 28 joints. This index can be calculated with the tender joint count (TJC), swollen joint count (SJC), erythrocyte sedimentation rate (ESR), and the visual analogue scale general well-being (VAS-GH).

The DAS28 can be calculated with the following formula:
**DAS28= 0.56*√TJC + 0.28*√SJC + 0.70*ln(ESR) + 0.014*VAS-GH**

The 28 joints which are evaluated within the TJC and SJC are shown in the Figure below.

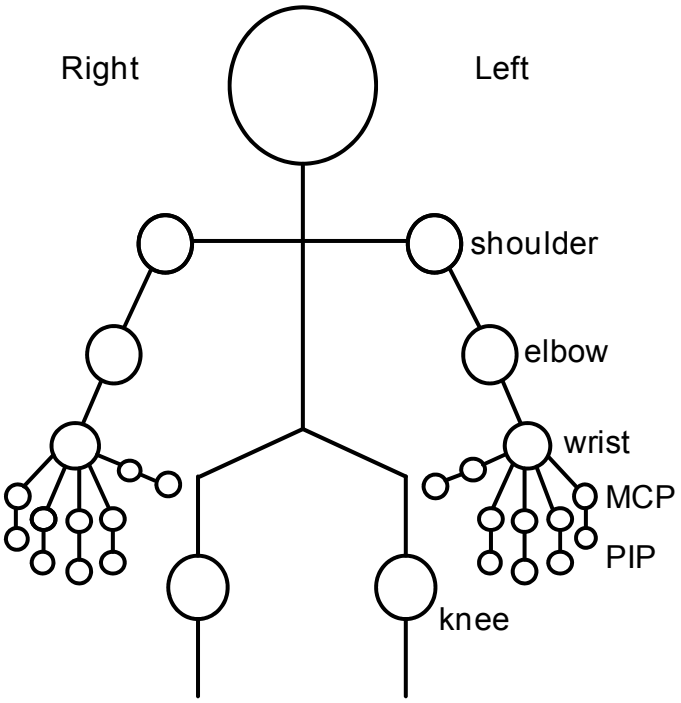
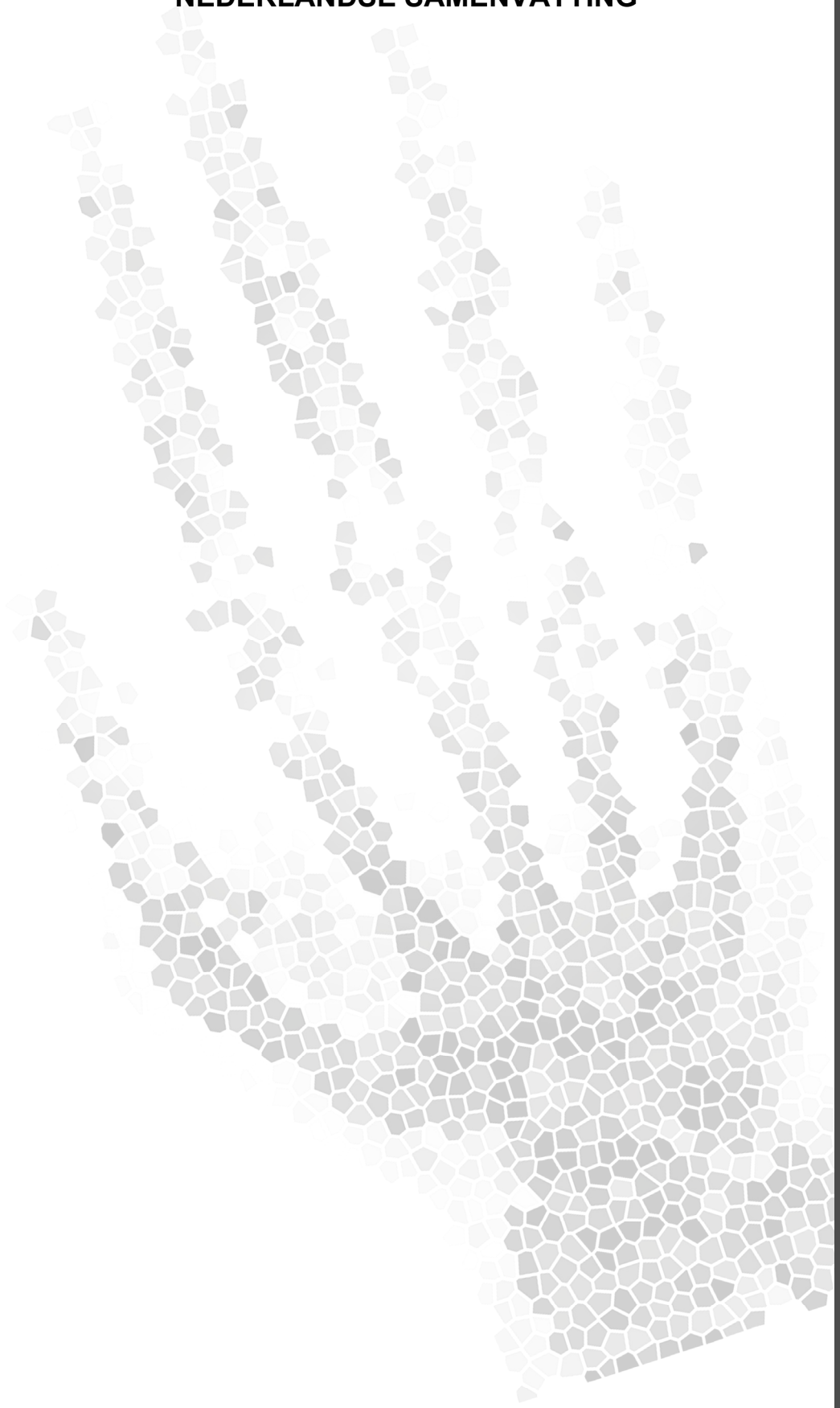



**Figure.** Disease activity score based on 28 joints (DAS28).
The joints, which are depicted as circles, are measured for the tender joint count (TJC) and swollen joint count (SJC) to calculate the DAS28.
MCP= metacarpophalangeal joints; PIP= proximal interphalangeal joints.

# NEDERLANDSE SAMENVATTING



## REUMATOÏDE ARTRITIS

Reumatoïde artritis (RA) is een chronische ziekte, waarbij met name de gewrichten zijn aangedaan. Door de ontsteking in de gewrichten, vooral in de handen en voeten, ervaren de patiënten veel pijn. Bij de behandeling van de ziekte is het belangrijk om niet alleen symptomen, zoals pijn en stijfheid te behandelen, maar ook om het ontstaan van schade aan gewrichten te vertragen en zo later in het ziektebeloop functionele beperking en gewrichtsoperaties zoveel mogelijk te voorkomen.

### Utrecht Artritis Cohort

Dit proefschrift beschrijft onderzoek dat is uitgevoerd binnen de Utrecht Artritis Cohort onderzoeksgroep, een langdurig samenwerkingsverband tussen het Universitair Medisch Centrum Utrecht en omliggende perifere ziekenhuizen*, dat in 1989 is gestart als de Stichting Reumaonderzoek Utrecht (SRU). Het eerste onderzoek binnen deze samenwerking liet zien dat het beste meteen nadat de diagnose van RA is vastgesteld, gestart kan worden met behandeling met “reumaremmers” (antireumatica, ook wel disease modifying anti-rheumatic drugs, DMARDs), die het ontstaan van schade aan gewrichten vertragen. Voorheen werd eerst gestart met ontstekingsremmende pijnstillers (nonsteroidal anti-inflammatory drugs, NSAIDs), die wel klachten onderdrukken, maar het ontstaan van schade aan gewrichten niet vertragen. Pas later werd zo nodig overgegaan op de behandeling met DMARDs. Deze behandelstrategie bleek duidelijk minder effectief in vergelijking met het meteen starten met DMARDs. Het tweede onderzoek binnen de SRU liet zien dat van de onderzochte DMARDs, methotrexaat (MTX) het beste resultaat gaf met betrekking tot effectiviteit en bijwerkingen, in vergelijking met twee andere DMARDs. Andere onderzoeksgroepen stelden dit ook vast. Dit was reden om in vervolgonderzoek MTX te gebruiken. Het vervolgonderzoek is Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA) genoemd en betreft op MTX gebaseerde behandelstrategieën. Dit onderzoek laat veelbelovende resultaten zien. Dit proefschrift is gebaseerd op verder onderzoek van vroege RA (patiënten waarbij RA recent is gediagnosticeerd) behandelstrategieën.

### Tight control behandelstrategie

Behandelstrategieën van RA en ook doelen van de behandeling zijn de afgelopen decennia sterk veranderd. Het ultieme doel van de behandeling van RA is uiteraard om de ziekte volledig te genezen. Omdat dit (nog) niet mogelijk is, is het doel van de behandeling volledige afwezigheid van ziekteverschijnselen (remissie) met zo weinig mogelijk schade aan de gewrichten. Om dit doel te bereiken worden steeds vaker behandelstrategieën toegepast volgens principes van ‘tight control’ en ‘treat to target’. Tight control kan worden

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gedefinieerd als een behandelstrategie waarbij er met medicatieaanpassingen (afhankelijk van de ziekteactiviteit bij de individuele RA patiënt) naar gestreefd wordt, in een zo kort mogelijke tijd lage ziekteactiviteit of remissie te bereiken. Dit principe wordt ook wel 'treat to target' genoemd, waarbij het target dan lage ziekteactiviteit of remissie is.

## DIT PROEFSCHRIFT

In het eerste deel van dit proefschrift worden effectiviteit, bijwerkingen en lange termijn resultaten van tight control beschreven. In het tweede deel wordt onderzoek naar mogelijke predictoren (voorspellers) van de ernst van RA beschreven, om onder- en overbehandeling van de individuele RA patiënt te voorkomen.

### Tight control

De eerste vraag die beantwoord wordt is of tight control een effectieve en haalbare strategie voor de behandeling van de RA patiënten is. Hiervoor zijn 4 gerandomiseerde tight control onderzoeken (FIN-RACo, TICORA, BeSt en CAMERA) bij patiënten met vroege RA bekeken (hoofdstuk 2). Deze onderzoeken laten zien dat het aantal patiënten in remissie hoger was in de groepen die behandeld werden volgens tight control dan in de groepen met minder intensieve behandeling. Hieruit kan geconcludeerd worden dat tight control een veelbelovend nieuw behandelprincipe is, niet alleen voor klinisch onderzoek, maar ook voor de dagelijkse praktijk.

Vaker toepassen van het tight control principe betekent gebruik van meer intensieve behandelstrategieën voor (vroege) RA patiënten. Dit zou kunnen leiden tot meer bijwerkingen. In hoofdstuk 3 is in het CAMERA onderzoek geanalyseerd of bijwerkingen een groter probleem waren bij patiënten met vroege RA die intensief behandeld werden met MTX volgens het tight control principe in vergelijking met bijwerkingen bij patiënten die minder intensief behandeld werden. Hoewel meer patiënten in de intensieve behandelstrategie bijwerkingen hadden, bleken de bijwerkingen relatief mild te zijn. Daarbij komt dat het effect in de intensieve behandelstrategie van CAMERA duidelijk beter was in vergelijking met dat van de conventionele strategie. Dit voordeel lijkt duidelijk op te wegen tegen het iets grotere risico op bijwerkingen. Deze resultaten ondersteunen het gebruik van intensieve behandeling met MTX voor patiënten met vroege RA in de dagelijkse praktijk.

Voor tight control kunnen verschillende manieren van ophogen van dosering van een medicijn en (combinaties van) verschillende soorten medicamenten toegepast worden als behandelstrategie om het gewenste doel (liefst remissie) te bereiken. In hoofdstuk 4 werd bekeken of de gebruikte behandelstrategie stappen in het CAMERA onderzoek effectief waren. Deze stappen zijn het intensiveren van de therapie door het geven van MTX als injectie (scMTX) in plaats van in de vorm van pillen, waardoor het lichaam meer MTX binnen krijgt. De tweede stap is het toevoegen van de DMARD cyclosporine aan de scMTX stap

indien de patiënt nog geen remissie heeft bereikt bij de maximaal (te verdragen) dosis MTX. De resultaten laten zien dat als MTX pillen onvoldoende effect hebben, scMTX als volgende stap verdere verbetering geeft, maar het toevoegen van cyclosporine niet. De scMTX stap kan dus aanbevolen worden om te gebruiken binnen een tight control behandelstrategie.

Gebaseerd op de eerste hoofdstukken van dit proefschrift luidt de conclusie dat tight control een goed behandelingsprincipe is op de korte termijn. Om de effectiviteit van deze strategie op de langere termijn te onderzoeken wordt in hoofdstuk 5 gekeken naar de lange termijn effecten van het CAMERA onderzoek, dat 2 jaar duurde en het effect van een intensieve (tight control) behandelstrategie vergeleek met dat van een conventionele strategie. Het bleek dat de verschillen in effect tussen de behandelstrategieën na 5 jaar behandeling niet meer te zien waren. Een verklaring zou kunnen zijn dat het tight control principe minder streng werd toegepast na het einde van het CAMERA onderzoek (na 2 jaar). Een goede reactie op de behandeling binnen 6 maanden na de start van de therapie binnen het CAMERA onderzoek bleek een onafhankelijke voorspeller van een beter resultaat na 5 jaar, ongeacht welke behandelstrategie de RA patiënt had gekregen. Deze resultaten geven aan dat waarschijnlijk langer moet worden doorgegaan met het tight control principe en dat bij patiënten met onvoldoende goede reactie op de behandeling vroeg in het ziektebeloop meer drastische veranderingen van de behandelstrategie nodig zijn dan alleen het ophogen van de medicatie.

De uitgevoerde tight control onderzoeken lieten goede resultaten zien, maar verbetering is mogelijk, vooral op het gebied van het aantal patiënten in remissie en de lange termijn resultaten. Als uitbreiding van de tight control behandelstrategie, zoals onderzocht in het CAMERA onderzoek, is in hoofdstuk 6 in een nieuw onderzoek bekeken of het toevoegen van prednison aan de op MTX gebaseerde tight control behandelstrategie voor de behandeling van patiënten met vroege RA extra voordeel biedt (CAMERA-II onderzoek). Dit bleek inderdaad het geval, zonder toename in bijwerkingen gedurende het 2 jaar durende onderzoek. Patiënten in de behandelstrategie met prednison bereiken in een vroegere fase van de ziekte remissie en hebben ook minder vaak toevoeging van een biologische DMARD (biological) nodig. Dit lagere gebruik van biologicals is belangrijk, omdat die middelen erg duur zijn en hoge kosten geven binnen de gezondheidszorg.

**Voorspelling van de ernst van RA**

Het tweede deel van het proefschrift betreft het voorspellen van de uitkomst van RA. De eerste onderzoeksvraag was of de dosis MTX, om bij een individuele RA patiënt een zo optimaal mogelijk resultaat te behalen, voorspeld zou kunnen worden. Veranderingen in de ziekteactiviteit in relatie met stapsgewijs ophogen van de dosis MTX werden onderzocht (hoofdstuk 7). De resultaten gaven aan dat de optimale MTX dosis wel globaal voorspeld kan worden, maar dat dit nog niet voldoende betrouwbaar is voor de individuele RA patiënt. Globaal genomen lijkt een startdosis van 15 mg/wk MTX een goede eerste keus te zijn.

Door regelmatig de ziekteactiviteit te meten bij stapsgewijs ophogen van MTX behandeling kan vastgesteld worden of verdere verbetering in de ziekteactiviteit verwacht kan worden of dat de behandelstrategie met een andere DMARD uitgebreid moet worden.

Bij tight control behandelstrategieën is het regelmatig vaststellen van de ziekteactiviteit belangrijk om het doel van lage ziekteactiviteit of remissie van RA te behalen. Door regelmatig de ziekteactiviteit vast te stellen kan gekeken worden of de patiënt aanpassingen nodig heeft in de behandeling (bijvoorbeeld bij een hoge ziekteactiviteit het toevoegen van andere medicatie, of bij een lage ziekteactiviteit het verlagen van de dosis). Dit is ook van belang om verdere schade aan de gewrichten (bot erosies) te voorkomen. Voor het meten van de ziekteactiviteit is de ziekteactiviteitsscore gebaseerd op 28 gewrichten (DAS28) één van de meest gebruikte instrumenten. De DAS28 is een scoresysteem voor de ziekteactiviteit van groepen van RA patiënten (bij medicijnenonderzoek) en is gebaseerd op het aantal aanwezige pijnlijke en gezwollen gewrichten van 28 te onderzoeken gewrichten (gemeten in de handen, pols, schouder en knieën), de bloedbezinking (als maat voor ontstekingsactiviteit) en op de score van de patiënt met betrekking tot het algemeen welbevinden (zie ook de appendix in dit proefschrift voor uitleg van de DAS28). Echter, het is nog niet duidelijk of dit instrument voor de individuele patiënt ook nauwkeurig de ziekteactiviteit weergeeft en daarmee de radiologische schade op termijn kan voorspellen. Daarom is de DAS28 als tight control meetinstrument onderzocht in dit proefschrift.

In hoofdstuk 8 is de invloed van tenderpoints (drukpijnlijke spieren en peesaanhechtingen) op de DAS28 bij patiënten met RA onderzocht. Het blijkt dat de DAS28 duidelijk wordt beïnvloed door de aanwezigheid van tenderpoints bij RA patiënten, doordat tenderpoints een sterke relatie hebben met het aantal pijnlijke gewrichten en het algemeen welbevinden van de patiënt. De meer objectieve onderdelen van de DAS28, namelijk het aantal gezwollen gewrichten en de bloedbezinking bleken niet gevoelig voor de aanwezigheid van tenderpoints. Bij aanwezigheid van tenderpoints (die vaak bij RA voorkomen) kan de score van de DAS28 dus meer ziekteactiviteit suggereren dan er in werkelijkheid is. Wanneer de DAS28 wordt toegepast bij tight control behandelstrategieën is het sterk aan te bevelen een volledige klinische evaluatie te doen, eventueel aanwezige tenderpoints na te gaan en de onderdelen van de DAS28 afzonderlijk te bekijken om een foutieve inschatting van de ziekteactiviteit door de DAS28 te herkennen.

Bij individuele RA patiënten kunnen verschillende gewrichten betrokken zijn bij de ziekte. Wanneer gebruik gemaakt wordt van de DAS28 als meetinstrument (waarbij de gewrichten van de voeten niet inbegrepen zijn), is het de vraag in hoeverre dit instrument geschikt is voor het voorspellen van de uitkomst van verschillende subgroepen van RA patiënten (bijvoorbeeld bij patiënten met voornamelijk RA in de handen of vooral in de voeten). In hoofdstuk 9 is bekeken of voor de subgroep van patiënten met voornamelijk ziekteactiviteit in de voeten, de met de DAS28 gemeten ziekteactiviteit nog goed overeenkomt met de

lange termijn uitkomsten. Het blijkt dat de DAS28 de ziekteactiviteit en de verwachtte gewrichtsschade in deze groep onderschat. Voor tight control behandelstrategieën in het bijzonder kan het gebruik van de DAS28 (of een ander instrument waarbij de voetgewrichten niet inbegrepen zijn) om de ziekteactiviteit van een individu te meten een probleem zijn. Voor het goed behandelen van individuele patiënten is het regelmatig vaststellen van de ziekteactiviteit in frequent bij RA betrokken gewrichten aanbevolen, vooral vroeg in het ziektebeloop. Ook het regelmatig beoordelen van de röntgenfoto's van handen en voeten blijft van belang.

Naast de klinische variabelen kunnen ook andere variabelen, zoals biomarkers gebruikt worden bij het voorspellen van de (lange termijn) uitkomst van RA. Onderzoek met betrekking tot dit onderwerp is in het laatste deel van dit proefschrift beschreven. In hoofdstuk 10 werd gekeken of de radiologische en klinische uitkomst op de lange termijn bij patiënten met vroege RA voorspeld zou kunnen worden door bot en kraakbeen biomarkers (C2C, C1,2C, CS846, CPII) die vroeg in het ziektebeloop werden bepaald. Sommige van deze biomarkers blijken iets voorspellende waarde voor de lange termijn uitkomst van vroege RA te hebben, maar veel minder in vergelijking met bekende klinische voorspellers.

Een combinatie van biomarkers zou mogelijk beter kunnen voorspellen dan individuele biomarkers zoals hierboven is beschreven. In het laatste hoofdstuk van dit proefschrift (hoofdstuk 11) is gekeken of een score gebaseerd op (plasmaconcentraties van) een specifieke set van biomarkers gerelateerd is aan de ziekteactiviteitsscore zoals met de DAS28 bepaald. Resultaten lieten zien dat de set biomarkers een redelijke overeenkomst heeft met de DAS28. Daarnaast kan de biomarkerscore patiënten met lage ziekteactiviteit identificeren. Hoewel deze set biomarkers redelijk goede resultaten behaalde, is meer onderzoek nodig om te kijken of deze set aanvullende waarde heeft binnen behandelstrategieën voor individuele RA patiënten.

**Conclusies**

De conclusie van het eerste deel van het proefschrift is dat tight control effectief en haalbaar is bij patiënten met (vroege) RA, vooral wanneer gestart wordt met een combinatie van MTX en een lage dosis prednison. Binnen deze behandelstrategie kwamen relatief milde bijwerkingen voor. Als stap in de behandelstrategie bij onvoldoende effect van de behandeling lijkt het omschakelen van MTX in pilvorm naar scMTX effectief, in tegenstelling tot het toevoegen van cyclosporine aan MTX. Bij onvoldoende reactie op de behandeling uiterlijk 6 maanden na het ontstaan van RA moet de strategie worden aangepast. Met tight control als behandelstrategie moet ook op de langere termijn worden doorgegaan.

De conclusie van het tweede deel van dit proefschrift over (lange termijn) voorspelling is dat om optimaal volgens het tight control principe te kunnen behandelen, goede methoden nodig zijn om de ziekteactiviteit te meten. De meest gebruikte maat, de DAS28, is als

meetinstrument voor de individuele patiënt nog niet optimaal. De aanwezigheid van tenderpoints beïnvloedt de ziekteactiviteitsscore als deze berekend wordt met de DAS28. De score is dan te hoog en dit zou kunnen leiden tot overbehandeling van de betreffende RA patiënt. Het gebruik van deze maat voor tight control kan ook leiden tot onderbehandeling van RA patiënten met vooral voetproblemen. Wanneer de DAS28 wordt toegepast bij tight control behandelstrategieën is het sterk aan te bevelen om een volledige klinische evaluatie te doen en eventueel aanwezige tenderpoints na te gaan, de onderdelen van de DAS28 ook afzonderlijk te bekijken en alle bij RA vaak betrokken gewrichten te onderzoeken (ook de voetgewrichten die niet bij de 28 gewrichten van de DAS28 horen), om patiënten niet onder of over te behandelen. Voor het optimaal toepassen van de tight control behandelstrategie zijn goede variabelen nodig voor het voorspellen van de uitkomst van RA. Het voorspellen van de meest optimale individuele dosis van MTX met klinische variabelen en het voorspellen van de ziekteactiviteit en radiologische uitkomst met biomarkers zijn nog niet klinisch toepasbaar. Voor het optimaal toepassen binnen een tight control behandelstrategie is verder onderzoek nodig.

# DANKWOORD

En dan nog…het dankwoord! Dit proefschrift is gebaseerd op data van grote reumatoïde artritis cohorten die de afgelopen jaren zijn verzameld en waarvoor een groot aantal mensen verantwoordelijk is geweest en inspanningen heeft geleverd.

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# CURRICULUM VITAE

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Maria Fokje (Marije) Bakker was born on the 17th of June 1983 in Heerenveen, the Netherlands. In 2001 she finished secondary school at the "Openbare Scholengemeenschap (OSG) Sevenwolden" in Heerenveen.
She studied Human Movement Sciences at the Rijksuniversiteit Groningen starting in September of that year. In November 2005 she obtained her Master of Science (MSc) degree.
For her study she did her master thesis investigating the gross motor development of children between 6 and 12 years old with mental disorders and learning disability under supervision of dr. E. Hartman and MSc S. Houwen at the department of Human Movement Sciences at the University Medical Center Groningen.
During the last year of the study she also developed a trainings program for racing cyclists, based on a literature study on the supervision of dr. M.T. Elferink-Gemser at the department of Human Movement Sciences at the University Medical Center Groningen.
A literature study on the influence of visual dependence of balance tests in elderly people and an investigation whether overtraining can be predicted in (top)sportsmen by a finger precuing task was done during the first years of the study at the department of Human Movement Sciences at the University Medical Center Groningen.
In September 2006 she started as a PhD student at the department of Rheumatology and Clinical Immunology at the University Medical Center Utrecht under supervision of dr. JWG Jacobs, prof.dr. FPJG Lafeber, and prof.dr. JWJ Bijlsma. To expand the epidemiological and statistical knowledge needed for the data analyses within this thesis, she also followed the post initial Master of Epidemiology at EpidM (EMGO) at the VU University Medical Center of Amsterdam.