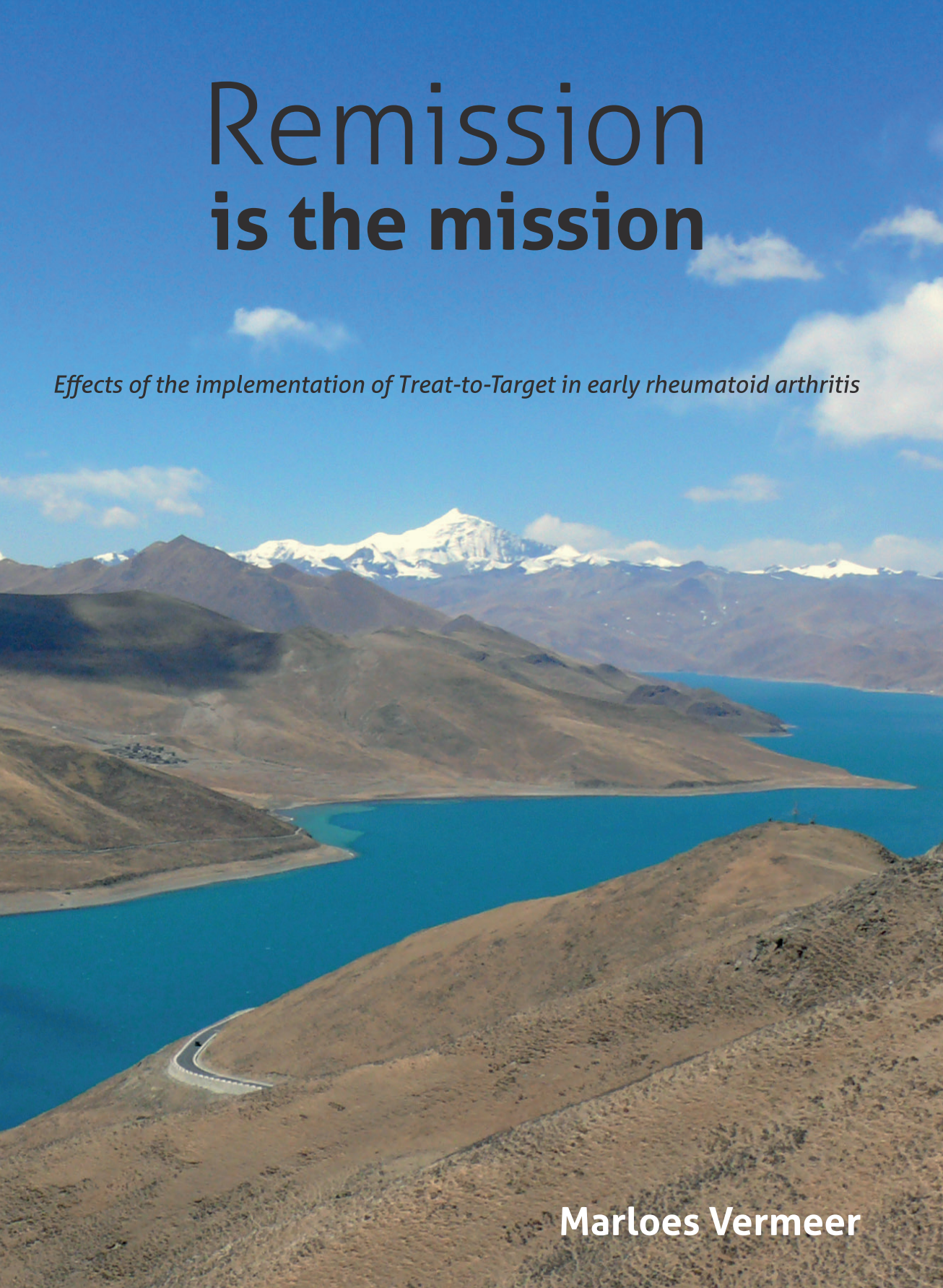
Remission
is the mission

Effects of the implementation of Treat-to-Target in early rheumatoid arthritis



Marloes Vermeer

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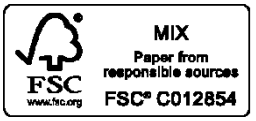

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EFFECTS OF THE IMPLEMENTATION OF TREAT-TO-TARGET IN EARLY RHEUMATOID ARTHRITIS

PROEFSCHRIFT

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Dit proefschrift is goedgekeurd door de promotoren prof. dr. M.A.F.J. van de Laar en prof. dr. P.L.C.M. van Riel en de assistent-promotor dr. H.H. Kuper.

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Contents

Chapter 1 |

General introduction

Rheumatoid arthritis

Rheumatoid arthritis (RA) is an autoimmune disease that is characterized by chronic inflammation of the joints (1). The prevalence is approximately 0.5-1.0% in the Western world (2). Women are three times more often affected than men and onset is most frequent between the ages of 40 and 70 (1).

RA has a major impact on the patient's physical and psychological health. Common symptoms of the disease are joint swelling, pain, morning stiffness and fatigue (1). The level of disease activity fluctuates over the course of the disease, varying from none to mild in periods of remission to severe in periods of exacerbation. RA is a progressive disease which can cause irreversible damage if not adequately treated (3), and which can greatly impair physical function (4) and quality of life. Extra-articular manifestations may occur, such as rheumatoid nodules, Sjögren's syndrome, and pulmonary and cardiovascular manifestations (5,6). When compared to the general population, RA is associated with increased mortality, the majority of which originates from cardiovascular diseases (7,8).

The disease not only places considerable burden on patients and their families, but also on healthcare systems and society as a whole (9-11). The economic burden goes beyond health care costs (12,13), with substantial losses in terms of work productivity due to absenteeism and lower presenteeism (14,15), which increase with disease duration (16).

Outcome measurement

Several measures of outcome are being used in the assessment of RA. The most frequently used measure of disease activity in Europe is the simplified form of the Disease Activity Score (DAS) (17), i.e. the DAS28 (18). The DAS28 has been extensively validated (19,20). This composite index includes a tender joint count in 28 joints (TJC28), a swollen joint count in 28 joints (SJC28), the erythrocyte sedimentation rate (ESR) and a patient's assessment of general health (GH), measured with a 100 mm visual analogue scale. The DAS28 is calculated using the following formula, resulting in a score ranging from approximately 0 to 10:

$$DAS28 = 0.56 * sqrt(TJC28) + 0.28 * sqrt(SJC28) + 0.70 * ln(ESR) + 0.014 * GH$$

Disease activity according to the DAS28 can be interpreted as remission (DAS28 < 2.6), low (2.6 ≤ DAS28 ≤ 3.2), moderate (3.2 < DAS28 ≤ 5.1), and high (DAS28 > 5.1).

The patient's functional status (disability) is often assessed by using the Health Assessment Questionnaire (HAQ) (21,22). The HAQ was developed for use in patients with a wide variety of rheumatic diseases, including RA. The most common measure used to assess a patient's quality of life is the 36-item Short Form Health Survey (SF-36) (23). The SF-36 is a generic measure of health status, covering both physical and mental aspects of health, which has been validated for use in RA (24). Quality of life generally refers to the patient's emotional, social and physical wellbeing, and his/her ability to function in the ordinary tasks of living. Other important patient reported outcomes in RA focus on pain and fatigue.

The progression of joint damage can be visualized with radiographs and can be quantified by several scoring techniques, e.g. the Larsen method (25), the Sharp method (26) and its modification by Van der Heijde (27). The Sharp-van der Heijde method has been widely used in clinical trials. This method assesses the presence and severity of damage (i.e. erosions and joint space narrowing) in individual joints in the hands and feet. It has been suggested that radiographs should be read in chronological order to increase sensitivity in detecting clinically relevant differences (28). When applying this scoring method, only progression can be scored. However, recently it has been suggested that healing of erosions might occur, which thus cannot be captured by this method (29-31).

Drug treatment

There is no known cure for RA. Therefore, the goal of treatment is to control disease activity and to achieve and maintain the lowest possible level of disease activity, ultimately remission. The treatment of RA has changed dramatically over the past decades, with strong consensus emerging in favor of early aggressive therapy. There is now abundant evidence that immediate initiation of adequate treatment is more efficacious than a delayed introduction (32). Inflammatory processes causing joint destruction appear to be triggered in the early stages of the disease and in this phase treatment has the potential to alter the disease process before irreversible damage occurs (32,33). In this therapeutic window of opportunity, the disease is thought to be more responsive to treatment (33,34).

Because it is now widely accepted that patients who are developing RA should receive therapy as soon as possible, early recognition of RA is of utmost importance. However, shortly after the onset of symptoms, a diagnosis can be difficult to make as the range of presentations is broad (1). Moreover, in a cohort of patients with undifferentiated early arthritis, RA may develop in some patients, whereas in others the arthritis may remit spontaneously, remain undifferentiated, or develop into other

rheumatic diseases (35). A modern treatment strategy of RA should focus on early referral to the rheumatologist, early diagnosis and early initiation of adequate treatment.

The anchor drug in the treatment of RA and often the drug of first choice is methotrexate (MTX) (36). Other conventional disease-modifying antirheumatic drugs (DMARDs), like sulfasalazine and hydroxychloroquine, are good alternatives in case of intolerance or failure to MTX. The benefits of DMARDs may be enhanced when the drugs are used in combination. Glucocorticoids, administered orally or by intra-articular or intra-muscular injections, are often used as bridging treatment until the full efficacy of a DMARD can be expected. Since the turn of the century, biological agents and especially the anti-tumour necrosis factor α (anti-TNFα) agents (e.g. adalimumab, etanercept and infliximab) have become available for the treatment of RA. Monotherapy of an anti-TNF agent as well as the combination of conventional DMARDs with an anti-TNF agent have emerged as highly successful (37-43). Over the past years, new effective biological agents, such as B-cell blockers (i.e. rituximab (44,45)), T-cell blockers (i.e. abatacept (46)) and anti-IL-6 (i.e. tocilizumab (47)) have been introduced in the treatment of RA. However, safety concerns and pharmaco-economical issues related to biological therapies are still debated.

In past decades, drug treatment of RA was managed using a pyramid approach that began with nonsteroidal anti-inflammatory drugs that were replaced by sequential conventional DMARDs if ineffective. A “reversed pyramid” approach now is favored, in which DMARDs are initiated early, rather than later in the treatment (48). Moreover, among other treatment strategies, a step-up approach has been proven to be effective, in which failure of initial DMARD monotherapy leads to combination therapy. Despite major recent advances in the treatment of RA, the optimal and most cost-effective therapy or treatment strategy has not yet been identified.

Definition of remission

The current goal of treatment of RA is to achieve sustained remission. It has been demonstrated that rapid attainment of remission can halt radiographic progression and improve functional ability (49). While, this emphasizes the importance of rapidly inducing and sustaining remission, the definition of remission is unclear. Over the last decade, several definitions of remission have been introduced: e.g. the preliminary criteria for clinical remission of the American Rheumatology Association (now the American College of Rheumatology (ACR)) (50), remission according to the DAS (17) and DAS28 (18), and remission based on the simplified and clinical disease activity indices (SDAI and CDAI, respectively) (51). In these definitions, different aspects of the disease are addressed and requirements with regard to treatment and duration of remission differ (52).

Consequently, the prevalence of remission varies substantially between definitions (53). This hinders interpretation of research findings and comparisons between studies.

Since there is need for uniform definitions of remission, the ACR and the European League Against Rheumatism (EULAR) recently proposed new definitions of remission in RA for clinical trials: a Boolean-based and an index-based definition (54). The Boolean-based definition requires fulfillment of the following four criteria: tender joint count ≤ 1, swollen joint count ≤ 1, C-reactive protein ≤ 1 mg/dL and patient global assessment (PGA) ≤ 1 (on a 0-10 scale). The index-based definition is defined as SDAI ≤ 3.3. However, even after the introduction of the new ACR/EULAR remission criteria, the definition of remission remains under debate (55-57).

Treat-to-target

A treat-to-target (T2T) (or tight control) approach has been widely advocated in the management of RA. This entails a treatment strategy tailored to the individual patient, which aims to control disease activity to predefined targets as quickly as possible, by protocolised adaptation of the treatment if the targets are not met. The concept of tight control has emerged from the management of hypertension (58) and diabetes (59) where it has proven to be highly effective. Over the past decade, several clinical trials have shown that the application of T2T is effective in RA: e.g. the Finnish Rheumatoid Arthritis Combination Therapy (FIN-RACo) study (60,61), the Tight Control of Rheumatoid Arthritis (TICORA) study (62), the Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA) study (63), the Behandel Strategieën (BeSt) study (40,64) and a pilot study of the intensified Combinatietherapie Bij Reumatoïde Artritis (COBRA) strategy (65).

With accumulating evidenced in support of T2T, current recommendations and guidelines on the management of RA now address the importance of treating RA to a target of remission or at least low disease activity (66-68). Figure 1 depicts the algorithm for treating RA to the primary target, i.e. (sustained) remission, or the alternative target, i.e. low disease activity in patients with long-standing disease, according to the T2T recommendations by the EULAR (68). It is evident that a T2T strategy should include monitoring of disease activity with appropriate frequency, using validated composite disease activity measures, such as the DAS28. Moreover, the application of tight control with protocolised treatment adjustments has been shown to have additional value with respect to clinical outcome compared with non-protocolised treatment adjustments (69).

Until now, the concept of targeting at remission has not yet been fully implemented in all rheumatology clinics and data on achieving remission in daily practice are scarce (70). In the routine care setting, disease activity is not consistently being measured using validated instruments (71) and medication is often not adapted when the

disease is still active (72-74). The question is whether the promising results from clinical trials applying T2T and aiming at remission can be generalized to the patients with RA seen in daily clinical practice. Clinical trials and daily clinical practice differ in several ways. The efficacy of treatment strategies achieved in clinical trials is hardly ever achieved in clinical practice (75-77). This observation can be explained by, among other factors, the restrictive inclusion criteria in clinical trials (for example with respect to age, disease activity and comorbidity), which severely limits the generalizability of the results to daily clinical practice (78,79). Observational data can provide important information regarding the effectiveness of treatment strategies in daily clinical practice, and are essential for making sound decisions regarding coverage and reimbursement (80).

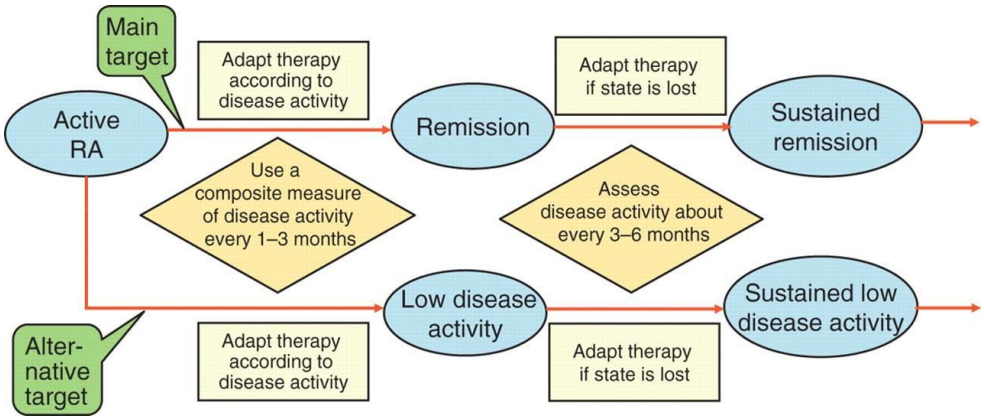

Figure 1. Algorithm for treating rheumatoid arthritis to target based on the European League Against Rheumatism (EULAR) recommendations.

Objective of this thesis

The general aim of this thesis is to evaluate the effects of the implementation of a T2T strategy aiming at remission in very early RA in daily clinical practice. For this purpose, data of the Dutch Rheumatoid Arthritis Monitoring (DREAM) remission induction cohort were used.

DREAM remission induction cohort

In January 2006, the DREAM remission induction cohort was started with the aim of developing, implementing and evaluating a T2T strategy aiming at remission in very early RA in daily clinical practice. The cohort was founded by the Arthritis Center Twente,

department of Rheumatology and Clinical Immunology, Medisch Spectrum Twente, Enschede, The Netherlands. The Rheumatology departments of the following hospitals joined later: Ziekenhuisgroep Twente, Almelo/Hengelo; Isala Klinieken, Zwolle; TweeSteden Ziekenhuis, Tilburg; University Medical Center Groningen, Groningen; and Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.

Consecutive patients newly diagnosed with RA were invited to participate in the cohort. Inclusion criteria were a clinical diagnosis of RA, symptom duration (defined as time from the first reported symptom to the diagnosis of RA by a rheumatologist) of one year or less, a DAS28 ≥ 2.6 and no previous treatment with DMARDs and/or prednisolone. Figure 2 presents the treatment strategy. Patients were evaluated at weeks 0, 8, 12, 20, 24, 36, and 52 and every 3 months thereafter. At each visit, disease activity was assessed using the DAS28. Therapy adjustments were protocolised and based on the DAS28 score, with intensification of treatment if the predefined targets (i.e., DAS28 < 2.6 for treatment with conventional DMARDs and DAS28 < 3.2 for treatment with anti-TNF agents) had not been met. If the target of a DAS28 < 2.6 was first met, medication was not changed. If the DAS28 was < 2.6 for at least six months, medication was gradually stepped down and eventually discontinued. Study recruitment was stopped in March 2012 but data collection is still ongoing.

The DREAM remission induction cohort is part of the DREAM registry. This multi-center registry has been including every RA patient who starts on an anti-TNF agent since February 2003. The aim of this registry is to evaluate the effectiveness, toxicity and use of anti-TNF agents in patients with RA in daily clinical practice.

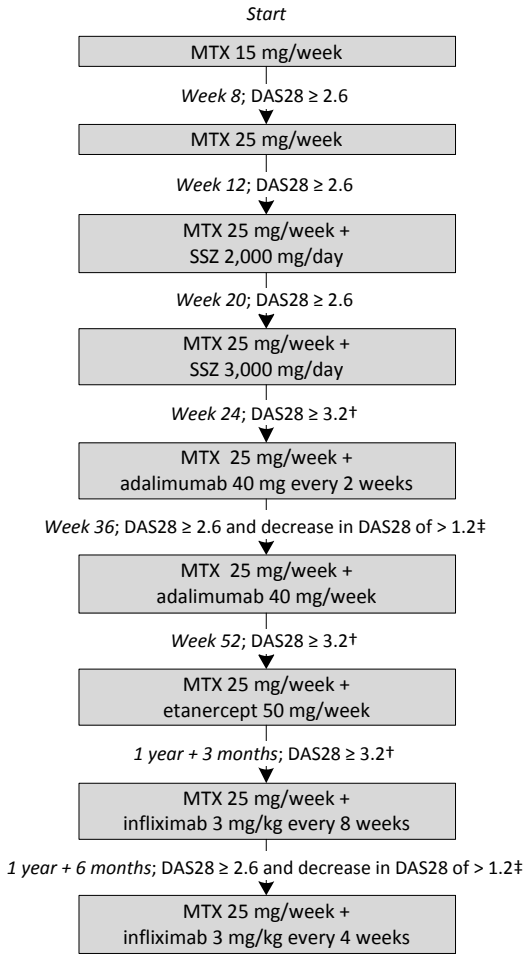

Figure 2. Treatment strategy of the Dutch Rheumatoid Arthritis Monitoring remission induction cohort.

SSZ = sulfasalazine.

† Anti-tumour necrosis factor α (anti-TNFα) therapy could be prescribed to patients with at least moderate disease activity (Disease Activity Score in 28 joints (DAS28) ≥ 3.2) and in whom treatment with at least two disease-modifying antirheumatic drugs had failed (including methotrexate (MTX) 25 mg/week).

‡ Anti-TNFα therapy could be continued only if the DAS28 had decreased by > 1.2 after 3 months.

Outline of this thesis

The first study that is presented in this thesis shows the clinical results of the T2T strategy aiming at remission at one year (**chapter 2**). The primary focus of this study was on the level of disease activity according to the DAS28, primarily remission. To verify the outcomes of the DAS28, additional disease activity outcomes were also evaluated.

In the following chapter (**chapter 3**), we investigated whether the T2T strategy was more effective than usual care for reaching remission after one year. For this purpose we compared the treatment effects of two treatment strategies derived from two different early RA cohorts.

The one year effectiveness of T2T was demonstrated in the above chapters. The question remained whether the effects of T2T sustain in the long-term. The aim of **chapter 4** was to evaluate the three year outcomes of the T2T strategy with respect to attainment of (sustained) remission, physical function, health-related quality of life and radiographic progression.

In **Chapter 5**, the adherence to the T2T recommendations was evaluated. We examined whether the T2T recommendations resulted in regular assessment of disease activity using the DAS28 and whether medication was adapted according to the protocolised treatment advice. Furthermore, we explored reasons for non-adherence to the T2T recommendations.

Chapter 6 presents the results of a cost-effectiveness and cost-utility analysis of T2T versus usual care. The concept of T2T assumes that intensive efforts and costs are made in the beginning of the disease to gain health and financial savings later. This chapter aims to answer the question whether the health benefits outweigh the assumed extra costs associated with performing a T2T approach.

In the DREAM remission induction cohort remission was defined as a DAS28 < 2.6. However, the prevalence of remission according to the provisional ACR/EULAR Boolean-based definition of remission was also investigated. One of the criteria in order to fulfill this definition of remission is that the patient must have a PGA score of 1 or less. Since it has frequently been observed that patients score higher on the PGA than would be expected on the basis of their clinical disease activity, it may be assumed that the PGA is not exclusively related to the clinical disease process of RA. In this case, it would be questionable whether a PGA score of ≤ 1 should be a prerequisite for remission. In **Chapter 7**, we therefore explored the relation between the PGA criterion of the new remission definition and the patient's clinical disease state.

Chapter 8 includes a summary and general discussion and conclusion. Moreover, we provide some further recommendations for future research.

References

1. Lee DM, Weinblatt ME**.** Rheumatoid arthritis. Lancet. 2001;358:903-11.
2. Scott DL, Wolfe F, Huizinga TW**.** Rheumatoid arthritis. Lancet. 2010;376:1094-108.
3. Welsing PM, Landewe RB, van Riel PL, Boers M, van Gestel AM, van der Linden S, et al. The relationship between disease activity and radiologic progression in patients with rheumatoid arthritis: a longitudinal analysis. Arthritis Rheum. 2004;50:2082-93.
4. Scott DL, Smith C, Kingsley G**.** Joint damage and disability in rheumatoid arthritis: an updated systematic review. Clin Exp Rheumatol. 2003;21(5 Suppl 31):S20-7.
5. Turesson C, Matteson EL**.** Management of extra-articular disease manifestations in rheumatoid arthritis. Curr Opin Rheumatol. 2004;16:206-11.
6. Symmons DP, Gabriel SE**.** Epidemiology of CVD in rheumatic disease, with a focus on RA and SLE. Nat Rev Rheumatol. 2011;7:399-408.
7. Symmons DP, Jones MA, Scott DL, Prior P**.** Longterm mortality outcome in patients with rheumatoid arthritis: early presenters continue to do well. J Rheumatol. 1998;25:1072-7.
8. Dadoun S, Zeboulon-Ktorza N, Combescure C, Elhai M, Rozenberg S, Gossec L, et al. Mortality in rheumatoid arthritis over the last fifty years: Systematic review and meta-analysis. Joint Bone Spine. 2012 (In press).
9. Kvien TK**.** Epidemiology and burden of illness of rheumatoid arthritis. Pharmacoeconomics. 2004;22(2 Suppl 1):1-12.
10. Boonen A, Severens JL**.** The burden of illness of rheumatoid arthritis. Clin Rheumatol. 2011;30 Suppl 1:S3-8.
11. Albers JM, Kuper HH, van Riel PL, Prevoo ML, van 't Hof MA, van Gestel AM, et al. Socio-economic consequences of rheumatoid arthritis in the first years of the disease. Rheumatology (Oxford). 1999;38:423-30.
12. Zhang W, Anis AH**.** The economic burden of rheumatoid arthritis: beyond health care costs. Clin Rheumatol. 2011;30 Suppl 1:S25-32.
13. Pugner KM, Scott DI, Holmes JW, Hieke K**.** The costs of rheumatoid arthritis: an international long-term view. Semin Arthritis Rheum. 2000;29:305-20.
14. Verstappen SM, Bijlsma JW, Verkleij H, Buskens E, Blaauw AA, ter Borg EJ, et al. Overview of work disability in rheumatoid arthritis patients as observed in cross-sectional and longitudinal surveys. Arthritis Rheum. 2004;51:488-97.
15. Braakman-Jansen LM, Taal E, Kuper IH, van de Laar MA**.** Productivity loss due to absenteeism and presenteeism by different instruments in patients with RA and subjects without RA. Rheumatology (Oxford). 2012;51:354-61.

16. Neovius M, Simard JF, Askling J. How large are the productivity losses in contemporary patients with RA, and how soon in relation to diagnosis do they develop? Ann Rheum Dis. 2011;70:1010-5.
17. van der Heijde DM, van 't Hof M, van Riel PL, van de Putte LB. Development of a disease activity score based on judgment in clinical practice by rheumatologists. J Rheumatol. 1993;20:579-81.
18. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. 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 Gestel AM, Haagsma CJ, van Riel PL. Validation of rheumatoid arthritis improvement criteria that include simplified joint counts. Arthritis Rheum. 1998;41:1845-50.
20. Fransen J, Creemers MC, Van Riel PL. Remission in rheumatoid arthritis: agreement of the disease activity score (DAS28) with the ARA preliminary remission criteria. Rheumatology (Oxford). 2004;43:1252-5.
21. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum. 1980;23:137-45.
22. Siegert CE, Vleming LJ, Vandenbroucke JP, Cats A. Measurement of disability in Dutch rheumatoid arthritis patients. Clin Rheumatol. 1984;3:305-9.
23. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30:473-83.
24. Tugwell P, Idzerda L, Wells GA. Generic quality-of-life assessment in rheumatoid arthritis. Am J Manag Care. 2007;13 Suppl 9:S224-36.
25. Larsen A. A radiological method for grading the severity of rheumatoid arthritis. Scand J Rheumatol. 1975;4:225-33.
26. Sharp JT. Radiologic assessment as an outcome measure in rheumatoid arthritis. Arthritis Rheum. 1989;32:221-9.
27. van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. J Rheumatol. 2000;27:261-3.
28. Bruynesteyn K, Van Der Heijde D, Boers M, Saudan A, Peloso P, Paulus H, et al. Detecting radiological changes in rheumatoid arthritis that are considered important by clinical experts: influence of reading with or without known sequence. J Rheumatol. 2002;29:2306-12.
29. Menninger H, Meixner C, Sondgen W. Progression and repair in radiographs of hands and forefeet in early rheumatoid arthritis. J Rheumatol. 1995;22:1048-54.

30. Sharp JT, Van Der Heijde D, Boers M, Boonen A, Bruynesteyn K, Emery P, et al. Repair of erosions in rheumatoid arthritis does occur. Results from 2 studies by the OMERACT Subcommittee on Healing of Erosions. J Rheumatol. 2003;30:1102-7.
31. Rau R. Is remission in rheumatoid arthritis associated with radiographic healing? Clin Exp Rheumatol. 2006;24(6 Suppl 43):S-41-4.
32. Quinn MA, Conaghan PG, Emery P. The therapeutic approach of early intervention for rheumatoid arthritis: what is the evidence? Rheumatology (Oxford). 2001;40:1211-20.
33. Nell VP, Machold KP, Eberl G, Stamm TA, Uffmann M, Smolen JS. 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.
34. Anderson JJ, Wells G, Verhoeven AC, Felson DT. Factors predicting response to treatment in rheumatoid arthritis: the importance of disease duration. Arthritis Rheum. 2000;43:22-9.
35. van Aken J, van Dongen H, le Cessie S, Allaart CF, Breedveld FC, Huizinga TW. Comparison of long term outcome of patients with rheumatoid arthritis presenting with undifferentiated arthritis or with rheumatoid arthritis: an observational cohort study. Ann Rheum Dis. 2006;65:20-5.
36. Pincus T, Yazici Y, Sokka T, Aletaha D, Smolen JS. Methotrexate as the "anchor drug" for the treatment of early rheumatoid arthritis. Clin Exp Rheumatol. 2003;21(5 Suppl 31):S179-85.
37. Lipsky PE, van der Heijde DM, St Clair EW, Furst DE, Breedveld FC, Kalden JR, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. N Engl J Med. 2000;343:1594-602.
38. Klareskog L, van der Heijde D, de Jager JP, Gough A, Kalden J, Malaise M, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet. 2004;363:675-81.
39. Keystone EC, Kavanaugh AF, Sharp JT, Tannenbaum H, Hua Y, Teoh LS, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. Arthritis Rheum. 2004;50:1400-11.
40. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJ, Hazes JM, 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.

41. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum. 2006;54:26-37.
42. van der Heijde D, Klareskog L, Rodriguez-Valverde V, Codreanu C, Bolosiu H, Melo-Gomes J, 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.
43. Emery P, Breedveld FC, Hall S, Durez P, Chang DJ, Robertson D, et al. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. Lancet. 2008;372:375-82.
44. Cohen SB, Keystone E, Genovese MC, Emery P, Peterfy C, Tak PP, et al. Continued inhibition of structural damage over 2 years in patients with rheumatoid arthritis treated with rituximab in combination with methotrexate. Ann Rheum Dis. 2010;69:1158-61.
45. Tak PP, Rigby WF, Rubbert-Roth A, Peterfy CG, van Vollenhoven RF, Stohl W, et al. Inhibition of joint damage and improved clinical outcomes with rituximab plus methotrexate in early active rheumatoid arthritis: the IMAGE trial. Ann Rheum Dis. 2011;70:39-46.
46. Kremer JM, Genant HK, Moreland LW, Russell AS, Emery P, Abud-Mendoza C, et al. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. Ann Intern Med. 2006;144:865-76.
47. Kremer JM, Blanco R, Brzosko M, Burgos-Vargas R, Halland AM, Vernon E, et al. Tocilizumab inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate: results from the double-blind treatment phase of a randomized placebo-controlled trial of tocilizumab safety and prevention of structural joint damage at one year. Arthritis Rheum. 2011;63:609-21.
48. Wilske KR, Healey LA**.** Remodeling the pyramid--a concept whose time has come. J Rheumatol. 1989;16:565-7.
49. van Tuyl LH, Felson DT, Wells G, Smolen J, Zhang B, Boers M**.** Evidence for predictive validity of remission on long-term outcome in rheumatoid arthritis: a systematic review. Arthritis Care Res (Hoboken). 2010;62:108-17.

50. Pinals RS, Masi AT, Larsen RA**.** Preliminary criteria for clinical remission in rheumatoid arthritis. Arthritis Rheum. 1981;24:1308-15.
51. 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.
52. Aletaha D, Smolen JS**.** Remission of rheumatoid arthritis: should we care about definitions? Clin Exp Rheumatol. 2006;24(6 Suppl 43):S-45-51.
53. Sokka T, Hetland ML, Makinen H, Kautiainen H, Horslev-Petersen K, Luukkainen RK, et al. Remission and rheumatoid arthritis: data on patients receiving usual care in twenty-four countries. Arthritis Rheum. 2008;58:2642-51.
54. Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LH, Funovits J, et al. American college of rheumatology/european league against rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Ann Rheum Dis. 2011;70:404-13.
55. Studenic P, Smolen JS, Aletaha D**.** Near misses of ACR/EULAR criteria for remission: effects of patient global assessment in Boolean and index-based definitions. Ann Rheum Dis. 2012;71:1702-5.
56. Masri KR, Shaver TS, Shahouri SH, Wang S, Anderson JD, Busch RE, et al. Validity and Reliability Problems with Patient Global as a Component of the ACR/EULAR Remission Criteria as Used in Clinical Practice. J Rheumatol. 2012;39:1139-45.
57. Kuriya B, Sun Y, Boire G, Haraoui B, Hitchon C, Pope JE, et al. Remission in Early Rheumatoid Arthritis -- A Comparison of New ACR/EULAR Remission Criteria to Established Criteria. J Rheumatol. 2012;39:1155-8.
58. Whitworth JA**.** 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. J Hypertens. 2003;21:1983-92.
59. Association AD**.** Standards of medical care in diabetes--2012. Diabetes Care. 2012;35 Suppl 1:S11-63.
60. Mottonen T, Hannonen P, Leirisalo-Repo M, Nissila M, Kautiainen H, Korpela 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.
61. Makinen H, Kautiainen H, Hannonen P, Mottonen T, Leirisalo-Repo M, Laasonen L, et al. Sustained remission and reduced radiographic progression with combination disease modifying antirheumatic drugs in early rheumatoid arthritis. J Rheumatol. 2007;34:316-21.

62. Grigor C, Capell H, Stirling A, McMahon AD, Lock P, Vallance R, 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.
63. Verstappen SM, Jacobs JW, van der Veen MJ, Heurkens AH, Schenk Y, ter Borg EJ, 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.
64. van der Kooij SM, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Guler-Yuksel M, Zwinderman AH, Kerstens PJ, et al. Drug-free remission, functioning and radiographic damage after 4 years of response-driven treatment in patients with recent-onset rheumatoid arthritis. Ann Rheum Dis. 2009;68:914-21.
65. van Tuyl LH, Lems WF, Voskuyl AE, Kerstens PJ, Garnero P, Dijkmans BA, et al. Tight control and intensified COBRA combination treatment in early rheumatoid arthritis: 90% remission in a pilot trial. Ann Rheum Dis. 2008;67:1574-7.
66. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines**.** Guidelines for the management of rheumatoid arthritis: 2002 Update. Arthritis Rheum. 2002;46:328-46.
67. Dutch Society of Rheumatology**.** Dutch guideline for diagnostics and treatment of rheumatoid arthrtis. 2009.
68. Smolen JS, Landewe R, Breedveld FC, Dougados M, Emery P, Gaujoux-Viala C, 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.
69. Schipper LG, van Hulst LT, Grol R, van Riel PL, Hulscher ME, Fransen J**.** 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.
70. Mierau M, Schoels M, Gonda G, Fuchs J, Aletaha D, Smolen JS**.** Assessing remission in clinical practice. Rheumatology (Oxford). 2007;46:975-9.
71. Pincus T, Segurado OG**.** Most visits of most patients with rheumatoid arthritis to most rheumatologists do not include a formal quantitative joint count. Ann Rheum Dis. 2006;65:820-2.
72. Fransen J, Moens HB, Speyer I, van Riel PL**.** 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.

73. van Hulst LT, Creemers MC, Fransen J, Li LC, Grol R, Hulscher ME, et al. How to improve DAS28 use in daily clinical practice?--a pilot study of a nurse-led intervention. Rheumatology (Oxford). 2010;49:741-8.
74. Harrold LR, Harrington JT, Curtis JR, Furst DE, Bentley MJ, Shan Y, et al. Prescribing practices in a US cohort of rheumatoid arthritis patients before and after publication of the American College of Rheumatology treatment recommendations. Arthritis Rheum. 2012;64:630-8.
75. Wolfe F, Michaud K**.** Towards an epidemiology of rheumatoid arthritis outcome with respect to treatment: randomized controlled trials overestimate treatment response and effectiveness. Rheumatology (Oxford). 2005;44 Suppl 4:iv18-iv22.
76. Zink A, Strangfeld A, Schneider M, Herzer P, Hierse F, Stoyanova-Scholz M, et al. Effectiveness of tumor necrosis factor inhibitors in rheumatoid arthritis in an observational cohort study: comparison of patients according to their eligibility for major randomized clinical trials. Arthritis Rheum. 2006;54:3399-407.
77. Kievit W, Fransen J, Oerlemans AJ, Kuper HH, van der Laar MA, de Rooij DJ, et al. The efficacy of anti-TNF in rheumatoid arthritis, a comparison between randomised controlled trials and clinical practice. Ann Rheum Dis. 2007;66:1473-8.
78. Sokka T, Pincus T**.** Most patients receiving routine care for rheumatoid arthritis in 2001 did not meet inclusion criteria for most recent clinical trials or american college of rheumatology criteria for remission. J Rheumatol. 2003;30:1138-46.
79. Sokka T, Pincus T**.** Eligibility of patients in routine care for major clinical trials of anti-tumor necrosis factor alpha agents in rheumatoid arthritis. Arthritis Rheum. 2003;48:313-8.
80. van Vollenhoven RF, Severens JL**.** Observational studies: a valuable source for data on the true value of RA therapies. Clin Rheumatol. 2011;30 Suppl 1:S19-24.

Chapter 2 |

Implementation of a treat-to-target strategy in very early rheumatoid arthritis. Results of the Dutch Rheumatoid Arthritis Monitoring remission induction cohort study

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Abstract

Objective. Clinical remission is the ultimate therapeutic goal in rheumatoid arthritis (RA). Although clinical trials have proven this to be a realistic goal, the concept of targeting at remission has not yet been implemented. The objective of this study was to develop, implement, and evaluate a treat-to-target strategy aimed at achieving remission in very early RA in daily clinical practice.

Methods. Five hundred thirty-four patients with a clinical diagnosis of very early RA were included in the Dutch Rheumatoid Arthritis Monitoring remission induction cohort study. Treatment adjustments were based on the Disease Activity Score in 28 joints (DAS28), aiming at a DAS28 of <2.6 (methotrexate, followed by the addition of sulfasalazine, and exchange of sulfasalazine with biologic agents in case of persistent disease activity). The primary outcome was disease activity after 6 months and 12 months of followup, according to the DAS28, the European League Against Rheumatism (EULAR) response criteria, and the modified American College of Rheumatology (ACR) remission criteria. Secondary outcomes were time to first DAS28 remission and outcome of radiography.

Results. Six-month and 12-month followup data were available for 491 and 389 patients, respectively. At 6 months, 47.0% of patients achieved DAS28 remission, 57.6% had a good EULAR response, and 32.0% satisfied the ACR remission criteria. At 12 months, 58.1% of patients achieved DAS28 remission, 67.9% had a good EULAR response, and 46.4% achieved ACR remission. The median time to first remission was 25.3 weeks (interquartile range 13.0-52.0). The majority of patients did not have clinically relevant radiographic progression after 1 year.

Conclusion. The successful implementation of this treat-to-target strategy aiming at remission demonstrated that achieving remission in daily clinical practice is a realistic goal.

Introduction

Clinical remission has proven to be an achievable therapeutic goal in patients with rheumatoid arthritis (RA) in the setting of randomized controlled trials. Ultimately, remission should be achieved in daily clinical practice as well, and, therefore, it has been proposed as the primary target of treatment in recent guidelines and recommendations for RA (1-3). Nevertheless, the concept of targeting at remission has not yet been implemented in all rheumatology units.

Remission of RA is associated with strongly reduced radiographic progression and improved functional ability (4). This emphasizes the importance of inducing rapid and sustained remission in RA. Keys to successful remission-inducing treatment are an early diagnosis, prompt therapeutic intervention, and intensive treatment. Shortly after the onset of symptoms, the differential diagnosis of arthritis can be difficult to make. RA develops in some patients, whereas in others the arthritis remits spontaneously, remains undifferentiated, or develops into other rheumatic diseases (5). However, early recognition of RA is important, because it is now widely accepted that patients in whom RA is destined to develop should begin receiving therapy as soon as possible.

Various findings support the importance of early intervention. First, it is consistent with the "therapeutic window of opportunity" hypothesis. Processes generating joint destruction appear to have been triggered in the early stages of the disease (6). In this phase, treatment has the potential to alter the disease process before irreversible damage is caused, thereby improving longterm outcomes in radiographic damage and functional ability (6,7). Second, many patients respond well to conventional disease-modifying antirheumatic drugs (DMARDs) in an early stage of the disease (8,9); such therapy approaches or even exceeds the level of effectiveness obtained with biologic agents (7). Third, there is an indication that after an excellent early response has been achieved, combination therapy can be successfully withdrawn without causing disease relapse (10-12).

Besides the use of combination therapy with DMARDs and biologic agents, a novel approach to intensive management of RA has been advocated: tight treatment to target (or tight control) (3). It has been consistently demonstrated that monitoring disease activity and subsequent adjustment of medication following a fixed protocol aiming at a predefined treatment goal is more beneficial than conventional treatment (13-15). Inspiring examples of strategy studies applying tight control are the Finnish Rheumatoid Arthritis Combination Therapy study (16,17), the TICORA (Tight Control of Rheumatoid Arthritis) study (18), the Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA) study (9), the BeSt (Behandel Strategieën) study (11,19), and a pilot trial of an intensified Combinatietherapie Bij Reumatoïde Artritis (COBRA) strategy (20). However,

these studies were performed in the setting of a randomized controlled trial, with strict inclusion and exclusion criteria, per-protocol treatment, and trial-dependent monitoring.

Until now, data on achieving disease remission in daily clinical practice are scarce (21). Therefore, the question is whether the promising results of randomized controlled trials can be generalized to the general population of patients with RA. Development and implementation of strategies to achieve remission in clinical care are warranted. Therefore, we conducted the Dutch Rheumatoid Arthritis Monitoring (DREAM) remission induction cohort study. The objective of this study was to develop, implement, and evaluate a treat-to-target regimen aiming at disease remission in very early RA. Here, we report the 1-year clinical results.

Patients and methods

Patients

Since January 2006, consecutive patients (ages ≥18 years) with newly diagnosed RA were invited to participate in the DREAM remission induction cohort study. Inclusion criteria were a clinical diagnosis of RA made at the discretion of the attending experienced rheumatologist, symptom duration (defined as time from the first reported symptom to the diagnosis of RA by a rheumatologist) of 1 year or less, a Disease Activity Score in 28 joints (DAS28; calculated using the erythrocyte sedimentation rate [ESR]) ≥2.6 (22), and no previous treatment with DMARDs and/or prednisolone. Patients were included in the study at the moment of diagnosis. The rheumatology clinics of 5 hospitals in The Netherlands collaborated in this study. The study protocol was submitted to the ethics committee of each participating hospital. Because the study contains data from daily clinical practice, the ethics committees determined, in accordance with Dutch law, that no approval was required. Nonetheless, patients were fully informed, and informed consent was obtained.

Treatment

Patients were evaluated at weeks 0, 8, 12, 20, 24, 36, and 52 and every 3 months thereafter. At every visit, disease activity was assessed with the DAS28. Therapy adjustments were protocolized and based on the DAS28, with intensification of treatment if the predefined targets (i.e., DAS28 <2.6 for treatment with conventional DMARDs and DAS28 <3.2 for treatment with anti-tumor necrosis factor α [anti-TNFα]) were not met.

At baseline, we prescribed all patients methotrexate (MTX) at an initial dosage of 15 mg per week (given orally). In case of an insufficient response, consecutive intensification steps with DMARDs included an increase in the dosage of oral MTX to 25

mg/week, the addition of oral sulfasalazine at a dosage of 2,000 mg/day, and an increase in the dose of sulfasalazine to 3,000 mg. In accordance with the guidelines of the Dutch Society of Rheumatology and Dutch reimbursement regulations, anti-TNFα therapy was prescribed for patients whose DAS28 remained ≥3.2. These subsequent steps included subcutaneous administration of adalimumab at a dosage of 40 mg every 2 weeks; an increase in the frequency of administration of adalimumab to every week in case of a DAS28 ≥2.6 and a decrease in the DAS28 of >1.2; exchange of adalimumab for subcutaneous etanercept at a dosage of 50 mg/week; exchange of etanercept for intravenous infliximab at a dosage of 3 mg/kg every 8 weeks after a loading dose at weeks 0, 2, and 6; and an increase in the frequency of administration of infliximab to every 4 weeks in case of a DAS28 ≥2.6 and decrease in the DAS28 of >1.2 (all in addition to MTX at a dosage of 25 mg/week). The full medication protocol is shown in Table 1. If the target of a DAS28 <2.6 was met, medication was not changed. If the DAS28 was <2.6 for at least 6 months, medication was gradually stepped down and eventually discontinued. In case of a disease flare (DAS28 ≥2.6), the most recently effective medication or medication dosage was restarted, and treatment could be subsequently intensified.

In individual patients with contraindications for specific medication, deviations from the protocol were allowed. In patients with an allergy to sulfa drugs (sulfonamides), sulfasalazine was replaced by oral hydroxychloroquine at a dosage of 400 mg/day. Nonsteroidal antiinflammatory drugs, prednisolone at a dosage of ≤10 mg/day, and intraarticular corticosteroid injections were allowed at the discretion of the attending rheumatologist.

Assessments

Baseline characteristics of the patients were collected, including age, sex, symptom duration, fulfillment of the American College of Rheumatology (ACR) 1987 criteria for the classification of RA (23), rheumatoid factor status, and anti-cyclic citrullinated peptide antibody status. Patients were assessed at the time of study entry and at every followup visit. Assessments included the tender joint count in 28 joints, the swollen joint count in 28 joints, the ESR, the C-reactive protein level, and the duration of morning stiffness. Patient-reported outcomes included global assessments of pain and general health on a 100-mm visual analog scale (VAS; 0 = best and 100 = worst); the disability index of the Dutch version of the Health Assessment Questionnaire, ranging from 0 to 3 (with high scores indicating more disability) (24,25); and component summary scores for physical and mental health on the 36-item Short Form Health Survey, ranging from 0 to 100 (with high scores indicating better health) (26). Data collection, including assessing the DAS28, was performed by well-trained rheumatology nurses.

Radiographs of the hands and feet were obtained at baseline and then annually. Radiographs were evaluated in chronologic order by 2 observers (MV and HHK), according to the modified Sharp/van der Heijde score (SHS) (27), and a consensus score was obtained. A patient was classified as having erosive disease if the erosion score was ≥1. Clinically relevant radiographic progression after 1 year was defined as an increase in the total SHS greater than the smallest detectable change, calculated as 4.3 points in the first year of followup (28).

Table 1. Treatment protocol*

Followup	DAS28	Medication
Week 0	≥2.6	MTX 15 mg/week
Week 8	≥2.6	MTX 25 mg/week
Week 12	≥2.6	MTX 25 mg/week + SSZ 2,000 mg/day
Week 20	≥2.6	MTX 25 mg/week + SSZ 3,000 mg/day
Week 24	≥3.2†	MTX 25 mg/week + ADA 40 mg every 2 weeks
Week 36	≥2.6 and decrease of >1.2‡	MTX 25 mg/week + ADA 40 mg/week
Week 52	≥3.2†	MTX 25 mg/week + etan. 50 mg/week
1 year + 3 months	≥3.2†	MTX 25 mg/week + inflix. 3 mg/kg every 8 weeks (after a loading dose at weeks 0, 2, and 6)
1 year + 6 months	≥2.6 and decrease of > 1.2‡	MTX 25 mg/week + inflix. 3 mg/kg every 4 weeks

* The goal of treatment was remission (Disease Activity Score in 28 joints [DAS28] <2.6). Treatment was intensified when this target was not met. In case of remission, medication was not changed. SSZ = sulfasalazine; ADA = adalimumab; etan. = etanercept; inflix. = infliximab.

† Following the guidelines of the Dutch Society of Rheumatology and Dutch reimbursement regulations, anti-tumor necrosis factor α (anti-TNFα) therapy could be prescribed to patients with at least moderate disease activity (DAS28 ≥3.2) and in whom treatment with at least 2 disease-modifying antirheumatic drugs had failed (including methotrexate [MTX] 25 mg/week).

‡ Anti-TNFα therapy could be continued only if the DAS28 had decreased by >1.2 after 3 months.

Study outcomes

The primary outcome was disease activity after 6 months and 12 months of followup. For the evaluation of disease activity, we used 3 sets of criteria: the DAS28, the European League Against Rheumatism (EULAR) response criteria (29), and the ACR preliminary criteria for clinical remission in RA (30). Disease activity according to the DAS28 was interpreted as remission (DAS28 <2.6), low (2.6 ≤ DAS28 ≤ 3.2), moderate (3.2 < DAS28 ≤ 5.1), and high (DAS28 >5.1). The EULAR response criteria classify patients as good responders, moderate responders, or nonresponders, depending on the extent of change

and the level of DAS28-defined disease activity reached. In this study, patients were followed up every 4-12 weeks, and fatigue was not assessed. Therefore, a modification of the ACR remission criteria was used, requiring 4 of the following 5 criteria: morning stiffness lasting ≤15 minutes, patient's global assessment of pain ≤10 mm on a VAS, no tender joints (28-joint count), no swollen joints (28-joint count), and normal ESR (<20 mm/hour in men and <30 mm/hour in women).

The secondary outcomes were time to the first moment of DAS28 remission and the radiographic outcome after 12 months of followup. A description of the medication being used at 12 months of followup was given.

Statistical analysis

Baseline characteristics of the patients are reported as the mean ± SD for normally distributed variables or as numbers with corresponding percentages for categorical variables. If variables were not normally distributed, values are reported as the median with the corresponding interquartile range (IQR). To test differences in baseline characteristics between subsets of patients, we used independent *t*-tests for normally distributed variables, chi-square tests for categorical variables, and Mann-Whitney U tests for non-normally distributed variables. *P* values less than 0.05 were considered significant.

Kaplan-Meier survival analysis was performed to assess time to the first moment of DAS28 remission. To ensure accuracy of the results, data from all followup visits were included in the Kaplan-Meier analysis. Statistical analyses were performed using SPSS version 17.0 software.

Results

From January 2006 to January 2010, a total of 534 patients were included in the cohort. The baseline characteristics of these patients are presented in Table 2. Patients were included at the moment of diagnosis. Therefore, disease duration was, per definition, 0 weeks. The study population consisted of patients with very early RA; the median duration of symptoms was 14.0 weeks (IQR 8.0-26.0 weeks). All patients had active disease with a mean ± SD DAS28 of 5.0 ± 1.1. Disease activity according to the DAS28 criteria was low in 6.4% of patients, moderate in 48.1% of patients, and high in 45.5% of patients.

Six-month data were available for 491 patients (91.9%), and 12-month data were available for 389 patients (72.8%) (Figure 1). Baseline characteristics of the patients included in the analyses of the 6-month and 12-month data were comparable with the characteristics of the total cohort population. In total, 17 patients were lost to followup for various reasons: death (n = 1), moving out of the area (n = 4), comorbidity (n = 9), and other (n = 3).

Table 2. Baseline characteristics of the patients (n = 534)*

Female sex	333 (62.4)
Age, mean ± SD years	58.6 ± 14.1
Symptom duration, median (IQR) weeks	14.0 (8.0-26.0)
Fulfillment of ACR 1987 criteria for RA	416/507 (82.1)
RF positive	318/524 (60.7)
Anti-CCP positive	281/488 (57.6)
RF negative and anti-CCP negative	158/498 (31.7)
ESR, median (IQR) mm/hour	28.5 (16.0-43.0)
CRP, median (IQR) mg/liter	13.0 (5.0-30.0)
No. of tender joints (28 assessed), median (IQR)	5.0 (2.0-9.0)
No. of swollen joints (28 assessed), median (IQR)	8.0 (4.0-12.0)
DAS28, mean ± SD	5.0 ± 1.1
Patient's assessment of pain, median (IQR) (0-100 VAS)	50.0 (36.0-70.0)
Patient's assessment of general health, median (IQR) (0-100 VAS)	50.0 (35.0-70.0)
HAQ score, median (IQR)	0.9 (0.5-1.4)
SF-36 PCS score, median (IQR)	35.8 (29.9-42.9)
SF-36 MCS score, median (IQR)	48.4 (38.5-58.3)

* Except where indicated otherwise, values are the number of patients/number of patients assessed (%).

IQR = interquartile range; ACR = American College of Rheumatology; RA = rheumatoid arthritis; RF = rheumatoid factor; anti-CCP = anti-cyclic citrullinated peptide; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; DAS28 = Disease Activity Score in 28 joints; VAS = visual analog scale; HAQ = Health Assessment Questionnaire; SF-36 = Short-Form 36 health survey; PCS = physical component summary; MCS = mental component summary.

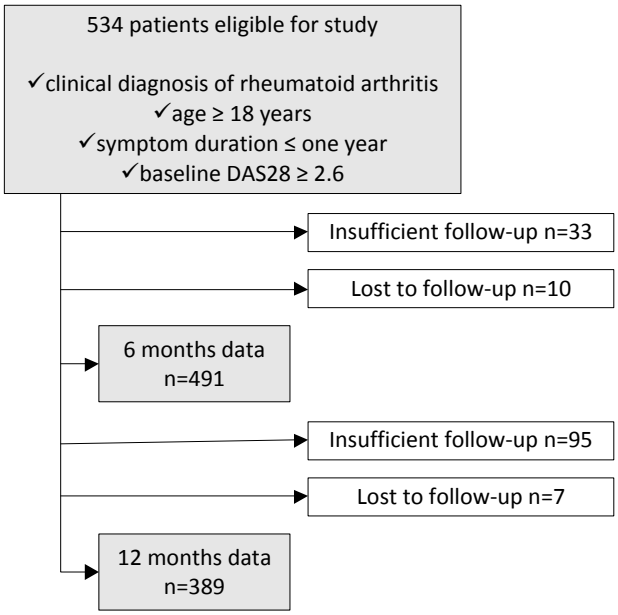

Figure 1. Study flow chart showing the number of patients included in the analyses for clinical outcomes after 6 months and 12 months and the number of patients lost to followup at different points in time.
DAS28 = Disease Activity Score in 28 joints.

DAS28

After 6 months of treatment to target, 47.0% of patients achieved the predefined goal of DAS28 remission (DAS28 <2.6). Low, moderate, and high disease activity was observed in 19.4%, 29.1%, and 4.5% of the patients, respectively. At the 12-month followup, 58.1% of patients had achieved DAS28 remission. Disease activity was low in 14.7%, moderate in 24.9%, and high in 2.3% of patients (Table 3).

EULAR response

After 6 months, a good EULAR response was observed in 57.6% of patients, response was moderate in 28.3%, and no response was observed in 14.1% of the patients. After 12 months, good, moderate, and no responses were observed in 67.9%, 23.9%, and 8.2% of the patients (Table 3).

ACR remission

ACR remission could be analyzed in 384 of 491 patients after 6 months and in 321 of 389 patients after 12 months (due to missing values for morning stiffness). After 6 months,

32.0% of these patients had achieved ACR remission. After 12 months, ACR remission had been achieved in 46.4% of these patients (Table 3).

Table 3. Clinical outcomes in the patients after 6 and 12 months of followup*

	6 months (n = 491)	12 months (n = 389)
DAS28 level		
Remission (DAS28 <2.6)	231 (47.0)	226 (58.1)
Low (2.6 ≤ DAS28 ≤ 3.2)	95 (19.4)	57 (14.7)
Moderate (3.2 < DAS28 ≤ 5.1)	143 (29.1)	97 (24.9)
High (DAS28 >5.1)	22 (4.5)	9 (2.3)
EULAR response		
Good	283 (57.6)	264 (67.9)
Moderate	139 (28.3)	93 (23.9)
None	69 (14.1)	32 (8.2)
ACR remission	123/384 (32.0)	149/321 (46.4)

* Values are the number (%).

American College of Rheumatology (ACR) remission could not be evaluated in all patients due to missing values for morning stiffness.

DAS28 = Disease Activity Score in 28 joints; EULAR = European League Against Rheumatism.

Time to remission

The time to the first occurrence of DAS28 remission was analyzed by Kaplan-Meier survival analysis. The estimate of the median time to this first moment of remission was 25.3 weeks (IQR 13.0-52.0 weeks).

Radiographic outcome

Radiographic data were available for a limited but random number of patients; radiographs at baseline and after 12 months were evaluated in 186 of the 389 patients with 1-year followup. At baseline, 48.4% of the patients had erosive disease, and the median total SHS was 2.0 (IQR 0.0-5.0). After 12 months, the median total SHS was 5.0 (IQR 2.0-10.0), and the median progression in the total SHS from baseline was 2.5 (IQR 1.0-5.0). Clinically relevant progression was observed in 26.9% of the patients. The percentage of patients without radiographic progression was different, although not yet reaching statistical significance, between the remission (n = 117) and non-remission (n = 69) groups (76.1% and 68.1%, respectively; $P = 0.237$).

Medication

Figure 2 presents actual medication use at the 12-month followup, stratified for remission state. In the remission group (n = 226), 59.3% of the patients were being treated with MTX monotherapy. MTX in combination with sulfasalazine was given to 22.6% of the patients, MTX with a biologic agent was given to 5.7% (5.3% received adalimumab, and 0.4% received infliximab), and other DMARD medication was prescribed in 8.0% of the patients. Low-dose prednisolone (≤10 mg/day) was added to the medication regimen in 8.4% of the patients, and 4.4% of the patients were medication-free.

In the non-remission group (n = 163), 32.5% of the patients received MTX monotherapy, 28.8% received MTX with sulfasalazine, 18.4% received MTX with a biologic agent (17.2% received adalimumab, and 1.2% received etanercept), and 13.5% were given other DMARD therapy. Prednisolone was added to the medication in 11.7% of the patients. Almost 7% of the patients were medication-free (mainly due to medication side effects).

In those patients who received prednisolone in addition to their other medication, prednisolone was mostly prescribed as bridging treatment. The most frequently used dosage was 5-10 mg/day. Figure 3 shows the influence of concomitant prednisolone therapy on achievement of remission. During the first year of followup, approximately one-fourth of patients received at least one intraarticular injection of corticosteroids.

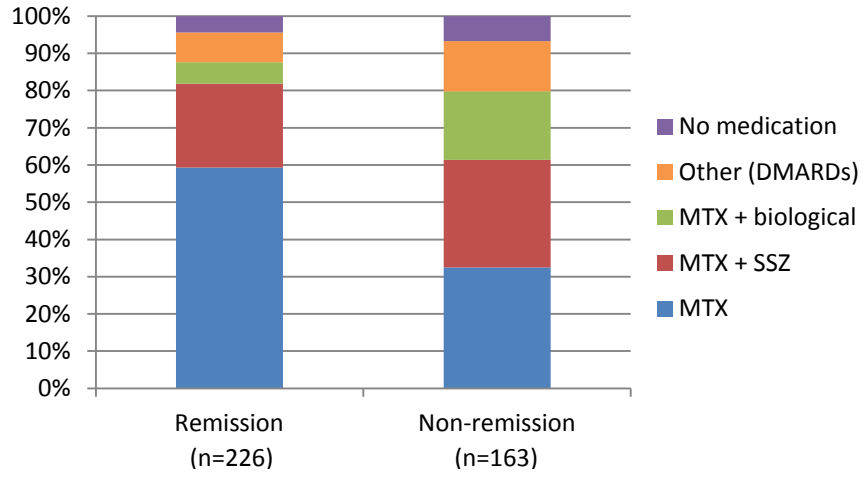

Figure 2. Actual medication use, stratified for the presence or absence of remission (defined as a Disease Activity Score in 28 joints of <2.6) after 12 months of followup.
Other (disease-modifying antirheumatic drugs [DMARDs]) treatment consisted mainly of either monotherapy or combination therapy with methotrexate (MTX), hydroxychloroquine, or sulfasalazine (SSZ).

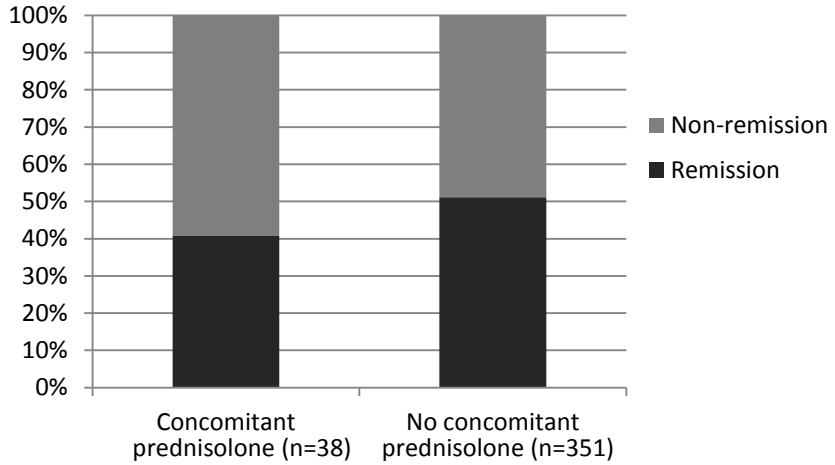

Figure 3. Remission (defined as a Disease Activity Score in 28 joints of <2.6), stratified for concomitant prednisolone treatment or no concomitant prednisolone, after 12 months of followup.

Discussion

The results of the current study show that achieving remission in very early RA in daily clinical practice using a treat-to-target strategy is a realistic goal. After 6 months and 12 months of followup, remission rates according to the DAS28 as well as the ACR criteria were high, and a good EULAR response rate was observed frequently. Moreover, remission was achieved rapidly. Preliminary results on radiographic outcome showed that the majority of patients did not have clinically relevant radiographic progression in the first year of followup. Therefore, targeting at remission should be adopted in clinical practice.

Remission has become an important outcome in clinical trials. However, there is little information about achieving remission in early RA under routine care conditions. It is assumed that the efficacy achieved in clinical trials is hardly ever achieved in clinical practice (31-33). This assumption can be explained by, among other factors, the restrictive inclusion criteria of clinical trials, as a result of which trials reflect only a minor proportion of the patients seen in clinical practice (34,35). In our cohort, in contrast, no stringent inclusion or exclusion criteria were used. As such, this study reflects the population of adults with very early RA as seen in daily clinical practice, irrespective of age, comorbidities, and disease activity. This study shows that treatment to target in combination with per-protocol treatment is feasible and successful in daily clinical practice. The implementation of such a treatment strategy depends on logistical and practical issues.

Treatment protocols aiming at remission evidently depend on national guidelines and local reimbursement regulations. Our study shows that MTX (monotherapy followed by combined treatment with other DMARDs when indicated) is highly successful in achieving this treatment goal. It is noteworthy that during the first year, anti-TNFα agents were prescribed for only ~10% of the patients. Concomitant prednisolone therapy did not contribute to the achievement of remission. Previously, the CAMERA study also showed that optimal use of MTX in a tight control setting leads to considerable improvement in disease activity in early RA (9).

This study has some limitations. First, the DAS28 has been subject to criticism, because joints in the feet are not included in measuring disease activity, and the DAS28 remission criterion is less stringent than that of, for example, the original DAS (36,37) and ACR remission criteria (38). To support the outcomes of disease activity measured with the DAS28, we presented additional outcomes such as the EULAR response criteria and ACR remission. Although the ACR remission criteria were slightly less frequently met, remission results according to the different definitions were comparably favorable. Second, the data used in this study are limited to a followup of 1 year. Long-term followup of the DREAM remission induction cohort is ongoing, which is critical for examining whether remission is sustained and for evaluating the long-term effects on radiographic progression and functional ability. Third, our results reflect the effects of only one medication strategy; no comparator was included. Other strategies will be evaluated in forthcoming cohorts.

The strengths of our study lie in the setting and design. First, the results of this study in daily clinical practice can be easily generalized to the entire population of patients with RA. Second, this cohort consists of a large number of patients with RA. Third, this study investigates a treatment strategy reflecting clinical practice. These are advantages of cohort data compared with those from clinical trials, in which generalizability of results is often limited, smaller numbers of patients are included, and the efficacy of only one drug is investigated. Fourth, our results appear robust and independent from definitions of remission. These first results of the DREAM remission induction cohort demonstrate, in contrast to previous clinical trials showing the efficacy of antirheumatic drugs, the effectiveness of a contemporary treatment strategy in rheumatology.

We defined very early RA as a duration of symptoms of ≤1 year in combination with immediate treatment at the moment of diagnosis. To our knowledge, this is the first study of very early RA. Other studies in early RA used durations as long as 1–2 years after the diagnosis to define early disease. However, this definition is not equivalent to the duration of disease, which extends back to the onset of symptoms. Our results underscore

the importance of immediate treatment after diagnosis. Moreover, the excellent results observed in this very early phase of disease support the window-of-opportunity theory.

In conclusion, we successfully implemented a treat-to-target and per-protocol treatment strategy aiming at remission in very early RA and demonstrated that achieving disease remission is a realistic goal in daily clinical practice. When remission is accepted as the therapeutic goal of RA, it is evident that disease management should include monitoring of disease activity and adjustment of therapy accordingly. We suggest a change in the current clinical approach to treating very early RA and believe that rheumatologists should make disease remission the mission for all patients.

Acknowledgements

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References

1. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis: 2002 update. Arthritis Rheum 2002;46:328-46.
2. Combe B, Landewe R, Lukas C, Bolosiu HD, Breedveld F, Dougados M, 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.
3. Smolen JS, Aletaha D, Bijlsma JW, Breedveld FC, Boumpas D, Burmester G, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis 2010;69:631-7.
4. Van Tuyl LH, Felson DT, Wells G, Smolen J, Zhang B, Boers M, for the American College of Rheumatology and the European League Against Rheumatism Committee to Define Remission for Clinical Trials. Evidence for predictive validity of remission on long-term outcome in rheumatoid arthritis: a systematic review. Arthritis Care Res (Hoboken) 2010;62:108-17.
5. Van Aken J, van Dongen H, le Cessie S, Allaart CF, Breedveld FC, Huizinga TW. Comparison of long term outcome of patients with rheumatoid arthritis presenting with undifferentiated arthritis or with rheumatoid arthritis: an observational cohort study. Ann Rheum Dis 2006;65:20-5.
6. Quinn MA, Conaghan PG, Emery P. The therapeutic approach of early intervention for rheumatoid arthritis: what is the evidence? Rheumatology (Oxford) 2001;40:1211-20.
7. Nell VP, Machold KP, Eberl G, Stamm TA, Uffmann M, Smolen JS. 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.
8. Anderson JJ, Wells G, Verhoeven AC, Felson DT. Factors predicting response to treatment in rheumatoid arthritis: the importance of disease duration. Arthritis Rheum 2000;43:22-9.
9. Verstappen SM, Jacobs JW, van der Veen MJ, Heurkens AH, Schenk Y, ter Borg EJ, et al, on behalf of the Utrecht Rheumatoid Arthritis Cohort study group. 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.
10. Quinn MA, Conaghan PG, O'Connor PJ, Karim Z, Greenstein A, Brown A, et al. Very early treatment with infliximab in addition to methotrexate in early, poor-prognosis rheumatoid arthritis reduces magnetic resonance imaging evidence of synovitis and

damage, with sustained benefit after infliximab withdrawal: results from a twelve-month randomized, double-blind, placebocontrolled trial. Arthritis Rheum 2005;52:27-35.

11. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJ, Hazes JM, 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.
12. Saleem B, Keen H, Goeb V, Parmar R, Nizam S, Hensor EM, et al. Patients with RA in remission on TNF blockers: when and in whom can TNF blocker therapy be stopped? Ann Rheum Dis 2010;69:1636-42.
13. Schoels M, Knevel R, Aletaha D, Bijlsma JW, Breedveld FC, Boumpas DT, et al. Evidence for treating rheumatoid arthritis to target: results of a systematic literature search. Ann Rheum Dis 2010;69:638-43.
14. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Kerstens PJ, Nielen MM, Vos K, van Schaardenburg D, et al. DAS-driven therapy versus routine care in patients with recent-onset active rheumatoid arthritis. Ann Rheum Dis 2010;69:65-9.
15. Schipper LG, van Hulst LT, Grol R, van Riel PL, Hulscher ME, Fransen J. 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.
16. Mottonen T, Hannonen P, Leirisalo-Repo M, Nissila M, Kautiainen H, Korpela M, et al, for the FIN-RACo trial group. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. Lancet 1999;353:1568-73.
17. Makinen H, Kautiainen H, Hannonen P, Mottonen T, Leirisalo- Repo M, Laasonen L, 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. Grigor C, Capell H, Stirling A, McMahon AD, Lock P, Vallance R, 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.
19. Van der Kooij SM, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Guler-Yuksel M, Zwinderman AH, Kerstens PJ, et al. Drugfree remission, functioning and radiographic damage after 4 years of response-driven treatment in patients with recent-onset rheumatoid arthritis. Ann Rheum Dis 2009;68:914-21.
20. Van Tuyl LH, Lems WF, Voskuyl AE, Kerstens PJ, Garnero P, Dijkmans BA, et al. Tight control and intensified COBRA combination treatment in early rheumatoid arthritis: 90% remission in a pilot trial. Ann Rheum Dis 2008;67:1574-7.

21. Mierau M, Schoels M, Gonda G, Fuchs J, Aletaha D, Smolen JS. Assessing remission in clinical practice. Rheumatology (Oxford) 2007;46:975-9.
22. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. 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.
23. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
24. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23:137-45.
25. Siegert CE, Vleming LJ, Vandenbroucke JP, Cats A. Measurement of disability in Dutch rheumatoid arthritis patients. Clin Rheumatol 1984;3:305-9.
26. Ware JE Jr, Sherbourne CD. The MOS 36-item Short-Form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473-83.
27. Van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method [corrected and republished in J Rheumatol 2000;27:261–3] J Rheumatol 1999;26:743-5.
28. Bruynesteyn K, Boers M, Kostense P, van der Linden S, van der Heijde D. Deciding on progression of joint damage in paired films of individual patients: smallest detectable difference or change. Ann Rheum Dis 2005;64:179-82.
29. Van Gestel AM, Prevoo ML, van 't Hof MA, van Rijswijk MH, van de Putte LB, van Riel PL. 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.
30. Pinals RS, Masi AT, Larsen RA, and the Subcommittee for Criteria of Remission in Rheumatoid Arthritis of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for clinical remission in rheumatoid arthritis. Arthritis Rheum 1981;24:1308-15.
31. Wolfe F, Michaud K. Towards an epidemiology of rheumatoid arthritis outcome with respect to treatment: randomized controlled trials overestimate treatment response and effectiveness. Rheumatology (Oxford) 2005;44 Suppl 4:iv18-22.
32. Zink A, Strangfeld A, Schneider M, Herzer P, Hierse F, Stoyanova- Scholz M, et al. Effectiveness of tumor necrosis factor inhibitors in rheumatoid arthritis in an observational cohort study: comparison of patients according to their eligibility for major randomized clinical trials. Arthritis Rheum 2006;54:3399-407.

33. Kievit W, Fransen J, Oerlemans AJ, Kuper HH, van der Laar MA, de Rooij DJ, et al. The efficacy of anti-TNF in rheumatoid arthritis, a comparison between randomised controlled trials and clinical practice. Ann Rheum Dis 2007;66:1473-8.
34. Sokka T, Pincus T. Eligibility of patients in routine care for major clinical trials of anti–tumor necrosis factor α agents in rheumatoid arthritis. Arthritis Rheum 2003;48:313-8.
35. Sokka T, Pincus T. Most patients receiving routine care for rheumatoid arthritis in 2001 did not meet inclusion criteria for most recent clinical trials or American College of Rheumatology criteria for remission. J Rheumatol 2003;30:1138-46.
36. Van der Heijde DM, van 't Hof M, van Riel PL, van de Putte LB. Development of a disease activity score based on judgment in clinical practice by rheumatologists. J Rheumatol 1993;20:579-81.
37. Landewe R, van der Heijde D, van der Linden S, Boers M. 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. Makinen H, Kautiainen H, Hannonen P, Sokka T. Is DAS28 an appropriate tool to assess remission in rheumatoid arthritis? Ann Rheum Dis 2005;64:1410-3.

Chapter 3 |

A tight control treatment strategy aiming for remission in early rheumatoid arthritis is more effective than usual care treatment in daily clinical practice: a study of two cohorts in the Dutch Rheumatoid Arthritis Monitoring registry

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Abstract

Objective. There is strong evidence from clinical trials that a 'treat to target' strategy is effective in reaching remission in rheumatoid arthritis (RA). However, the question is whether these results can be translated into daily clinical practice and clinical remission is a reachable target indeed. The study aims to investigate whether in early RA a treatment strategy aiming at Disease Activity Score (DAS) 28 <2.6 is more effective than 'usual care' treatment for reaching clinical remission after 1 year.

Methods. Two early RA inception cohorts from two different regions including patients who fulfilled the American College of Rheumatology criteria for RA were compared. Patients in the tight-control cohort (n=126) were treated according to a DAS28-driven step-up treatment strategy starting with methotrexate, addition of sulphasalazine (SSZ) and exchange of SSZ by anti-tumour necrosis factor in case of failure. Patients in the usual care cohort (n=126) were treated with methotrexate or SSZ, without DAS28-guided treatment decisions. The primary outcome was the percentage remission (DAS28<2.6) at 1 year. Time to first remission and change in DAS28 were secondary outcomes.

Results. After 1 year, 55% of tight-control patients had a DAS28<2.6 versus 30% of usual care patients (OR 3.1, 95% CI 1.8 to 5.2). The median time to first remission was 25 weeks for tight control and more than 52 weeks for usual care (p<0.0001). The DAS28 decreased with -2.5 in tight control and -1.5 in usual care (p<0.0001).

Conclusion. In early RA, a tight control treatment strategy aiming for remission leads to more rapid DAS28 remission and higher percentages of remission after 1 year than does a usual care treatment.

Introduction

The ultimate goal in rheumatoid arthritis (RA) treatment is to achieve and sustain clinical remission as early as possible in order to prevent joint damage and functional disability (1-3). Current treatment approaches include early and intensive treatment, which are believed to be essential to achieve early remission and to provide a better clinical outcome of RA treatment (4-11).

Several clinical trials have demonstrated that applying a tight control strategy is effective in reducing disease activity, disability and progression of joint damage (7,12-14). Tight control in RA is defined as optimising treatment by measurement of disease activity in order to make treatment adjustments to reach a predefined target, notably low disease activity or clinical remission (15-17). It is suggested that disease activity measurement in combination with a treatment protocol is more effective than tight control without protocol-driven treatment changes (18). However, the question is whether these results of clinical trials of tight control indeed can be translated into daily clinical practice.

Therefore, two inception cohorts from two different regions were used to study the effect of tight control versus 'usual care' in early RA: one tight-control cohort with remission as treatment goal and one usual-care cohort. Cohort data from daily clinical practice are of value to investigate the effects of interventions in daily practice, including the effects of tight control (19,20). The patients included in a clinical cohort are supposed to be representative of the population with RA, and they are treated under daily practice circumstances.

The aim of this study was to investigate in early RA whether a tight control treatment strategy is more effective than treatment according to usual care in reaching remission after 1 year, in daily clinical practice cohorts.

Methods

Study design

For the aim of this quasi-experimental study, patients were selected from two distinct early RA inception cohorts from outpatient clinics in two different regions in The Netherlands, where all patients with RA are treated by clinic based rheumatologists. In the 'tight control' cohort, regular evaluation of disease activity was applied in combination with protocolised treatment adjustments aiming for remission (21). In the usual care cohort, patients were treated according to daily clinical practice, with regular evaluation of disease activity but without protocolised treatment adjustments (22). Each patient gave informed consent before the inclusion in the inception cohorts, and the responsible local

medical ethics committee had approved the study protocols of both cohorts. The inclusion and the data collection are still ongoing.

Data selection

In both cohorts, patients with early RA were included according to the following inclusion criteria: meeting the 1987 revised American College of Rheumatology classification criteria for RA (23), age ≥18 years, disease duration less than 1 year and no previous treatment with disease modifying antirheumatic drugs (DMARDs) or prednisolone. Patients were included at diagnosis. For the current study, all included patients had a complete Disease Activity Score based on 28 joint counts (DAS28) at baseline, had a minimal follow-up time of 48 weeks and were not in remission at baseline.

Tight control

Since January 2006, consecutive patients with early RA were enrolled in the Dutch Rheumatoid Arthritis Monitoring remission induction cohort study. The rheumatology clinics of three hospitals in The Netherlands – Medisch Spectrum Twente, Enschede; Ziekenhuisgroep Twente, Almelo/Hengelo; and Isala Klinieken, Zwolle – participated in this study.

Patients visited the clinic at weeks 0, 8, 12, 20, 24, 36 and 52, and every 3 months thereafter. Treatment adjustments were standardised and protocolised, aiming at remission using the DAS28 with DAS28<2.6 as cut point. Patients started treatment with methotrexate (MTX) 15 mg/week upon diagnosis. In case of inefficacy, the consecutive intensification steps with DMARD medication were, at week 8, increase in MTX dose to 25 mg/week; at week 12, addition of sulphasalazine (SSZ) 2000 mg/day; and at week 20, increase in SSZ dose to 3000 mg. In accordance with the Dutch guidelines, anti-tumour necrosis factor (TNF) treatment was prescribed for patients whose DAS28 remained ≥3.2. These subsequent steps included, at week 24, adalimumab 40 mg every 2 weeks; at week 36, frequency increase of adalimumab to every week; at week 52, exchange of adalimumab for etanercept 50 mg per week; after 1 year and 3 months, infliximab 3 mg/kg bodyweight every 8 weeks; and after 1 year and 6 months, frequency increase of infliximab to every 4 weeks.

If the remission target of DAS28<2.6 was met, medication was not changed. In case of sustained remission (≥6 months) the most recently added drug would be tapered.

Non-steroidal anti-inflammatory drugs (NSAIDs), prednisolone at ≤10 mg/day and intra-articular corticosteroid injections were allowed at the discretion of the attending rheumatologist.

Usual care

In the usual-care cohort, patients were visiting (between March 2005 and 2008) the outpatient clinic of the rheumatology departments of the Radboud University Nijmegen or of the Maartenskliniek in Nijmegen, The Netherlands.

In this cohort, all patients were regularly assessed using the DAS28 at weeks 0, 12, 24, 36 and 52, but treatment decisions could be made at any time, according to the discretion of the treating rheumatologist. Patients were treated with conventional DMARDs and/or biologicals following the guidelines for RA (24,25). A common strategy applied was starting with MTX mono treatment, subsequently switching to SSZ or adding SSZ in case of MTX failure, and adding an anti-TNF agent after two or more DMARDs failed, in accordance with the Dutch guidelines. Also, NSAIDs and prednisolone (oral or injections) could be used at the discretion of the attending rheumatologist.

Clinical assessments

The following variables were collected at baselines: age, sex, disease duration, symptom duration, anti-cyclic citrullinic peptide positivity and rheumatoid factor positivity. Clinical assessments included the DAS28 every 3 months and the Dutch version of the disability index of the Health Assessment Questionnaire (HAQ) every 6 months (26,27). Research nurses assessed the variables needed for the DAS28 (26). Other clinical variables assessed were patient rating for pain on a 100 mm Visual Analogue Scale and C reactive protein (mg/l). Changes in DMARD and/or biological treatment and concomitant treatments with prednisolone (oral/intramuscular) and/or NSAIDs were standardly registered during follow-up.

Outcome measures

The primary outcome of this study was the percentage remission (DAS28 <2.6) at 1 year after the baseline. Secondary outcome measures were time to achieve remission, the course over time of the DAS28, the percentage of patients with 'low' disease activity (DAS28≤3.2), the mean change in DAS28 and individual core set variables from baseline to 1 year (28).

Sample size estimation

Sample size was estimated for the primary outcome measure, percentage remission (DAS28<2.6) at 1 year. It was aimed to detect a clinically relevant difference in remission of 20% between both groups, assuming that tight control would show more effectiveness than usual care. Applying an α of 0.05 (conventionally two-sided) and a 1-β ('power') of 0.90, the necessary sample size was estimated to be at least 2×125=250 patients.

Consequently, 126 patients were included from the tight control cohort, and 126 from the usual care cohort.

Statistical analyses

Logistic regression analysis was performed to test whether there was a between group difference in the occurrence of remission according to a DAS28<2.6 (primary outcome). Confounder correction was applied by adding potential confounders to the logistic regression model using 10% change in the main effect as selection criterion. Further, it was analysed whether the effect between treatment groups would be dependent of symptom duration (≤18 weeks vs >18 weeks) (29).

Kaplan-Meier survival curves and Cox proportional hazards regression modelling including confounder correction were used to analyse a between-group difference in time to achieve remission. The course over time of the DAS28 in both groups was analysed using longitudinal linear regression (mixed models), correcting for repeated measurements using an autoregressive covariance structure. Treatment with DMARDs, anti-TNF and prednisolone was described for both groups.

The level of significance was set at a two-sided *p* value less than 0.05. The statistical analyses were carried out using the Statistical Package for the Social Sciences (version 16.0).

Results

Baseline variables

Both treatment groups were similar at baseline (Table 1) regarding age and gender, as well as for time since diagnosis and baseline DAS28; nearly half of the patients had high disease activity (DAS28>5.1). The symptom duration was lower, while HAQ, patient's rating of pain and patient's global assessment of disease activity were higher in the tight control group.

Remission

After 1 year, 55% of tight-control patients were in DAS28 remission compared to 30% of usual-care patients (p<0.0001), (Figure 1A). The OR was 3.1 (95% CI 1.8 to 5.2) adjusted for baseline DAS28; there were no confounders. Accordingly, patients treated according to tight control had about a three times higher odds to have a DAS28<2.6 1 year after the baseline. There were no patients in 6 months remission for whom medication could be suspended.

Table 1. Demographic and baseline disease characteristics.

	Tight control (n = 126)	**Usual care (n = 126)**	***p* Value***
Age (mean (±SD), years)	56 (13)	57 (14)	0.57
Time since symptoms (median (IQR), weeks)	15 (8-26)	18 (9-37)	0.042
Time since diagnosis (median (IQR), weeks)	0 (0-0)	0 (0-0)	0.99
Women (n (%))	78 (62%)	77 (61%)	0.89
Rheumatoid factor positive (n (%))	79 (63%)	93 (74%)	0.058
Anti-cyclic citrullinic peptide positive (n (%))	71 (64%)	69 (62%)	0.78
DAS28 (mean (SD))	5.0 [1.2]	4.8 (1.1)	0.13
HAQ score (median (IQR))	1.1 (0.8-1.5)	0.9 (0.5-1.3)	0.002
Swollen joint count (median (IQR))	8 (5-12)	8 (5-12)	0.63
Tender joint count (median (IQR))	5 (2-10)	4 (2-9)	0.25
ESR (median (IQR), mm/h)	28 (14-44)	29 (18-44)	0.69
CRP (median (IQR), mg/l)	11 (5-34)	9 (0-31)	0.15
VAS pain, 0-100 (mean (SD), mm)	53 (23)	45 (22)	0.006
VAS GH, 0-100 (mean (SD), mm)	53 (24)	44 (22)	0.003

IQR P25-P75.

**p* value for between group comparisons.

CRP, C reactive protein; DAS28, Disease Activity Score based on 28 joint counts; ESR, erythrocyte sedimentation rate; GH, general health; HAQ, Health Assessment Questionnaire; VAS, Visual Analogue Scale.

Symptom duration and remission

The study sample was split in two equal subsamples according to median symptom duration (18 weeks). In patients with a short symptom duration (n=126), 57% of tight-control patients were in DAS28 remission compared to 43% of usual-care patients (p=0.041), with an OR of 2.2 (95% CI 1.0 to 4.7), (Figure 1B). In patients with longer symptom duration (n=126), 52% of tight-control-treated patients and 21% of usual-care-treated patients were in remission (p<0.0001), with an OR of 4.1 (95% CI 1.9 to 8.9).

Low disease activity

In the tight-control group, there were more patients reaching low disease activity (p<0.0001) than in the usual-care group (Figure 1A). In the tight-control group, 75% had low disease activity, 22% had moderate disease activity and 3% had high disease activity. In the usual care group, 42% of patients had low disease activity, 49% had moderate disease activity and 9% had high disease activity.

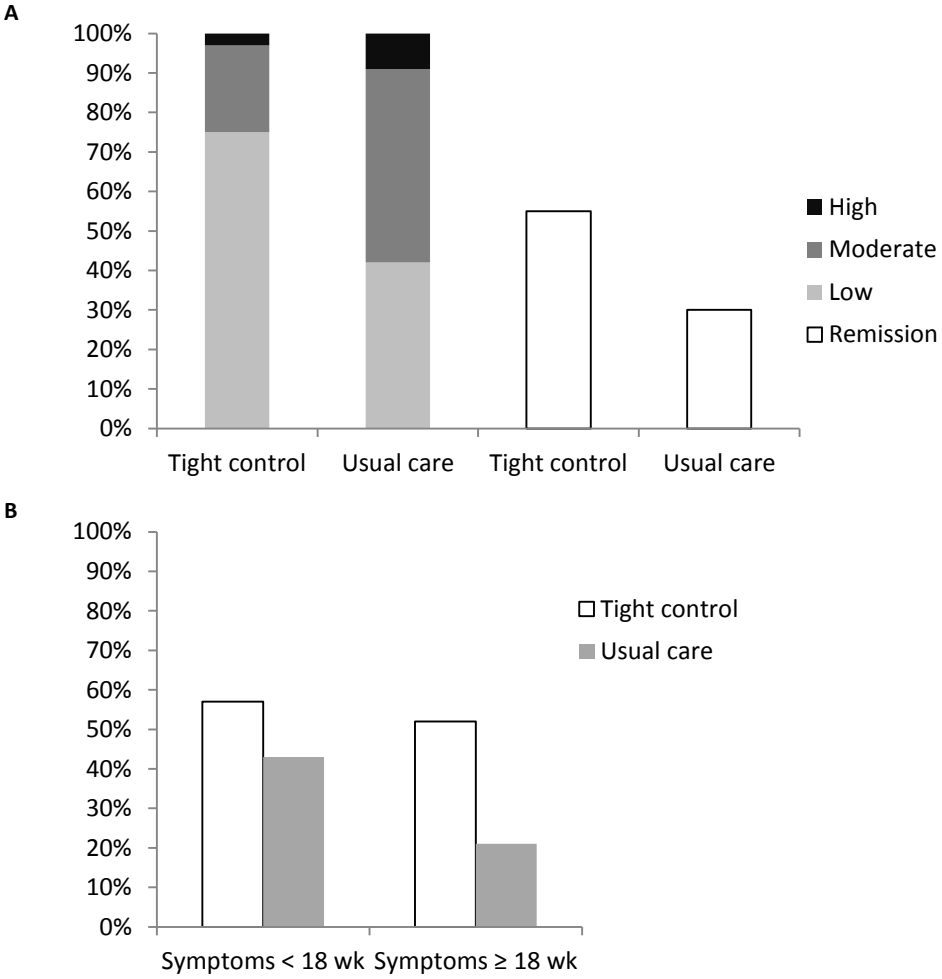

Figure 1. Remission and disease activity levels after 1 year. (A) Remission (DAS28<2.6) and levels of low (DAS28≤3.2), moderate (3.2<DAS28≤5.1) and high (5.1<DAS28) disease activity at 12 months of tight-control and usual-care groups. (B) Remission at 12 months in tight-control and usual-care groups, by equal subgroups of short (18 weeks) and longer (>18 weeks) symptom duration.
DAS28, Disease Activity Score based on 28 joint counts.

Time to achieve remission

Time to remission (DAS28<2.6) was significantly shorter in the tight-control group than in the usual-care group, with a median of 25 weeks versus a median over 52 weeks (p<0.0001), (Figure 2). Already after 8 weeks, the survival curve of the tight control group appeared to diverge.

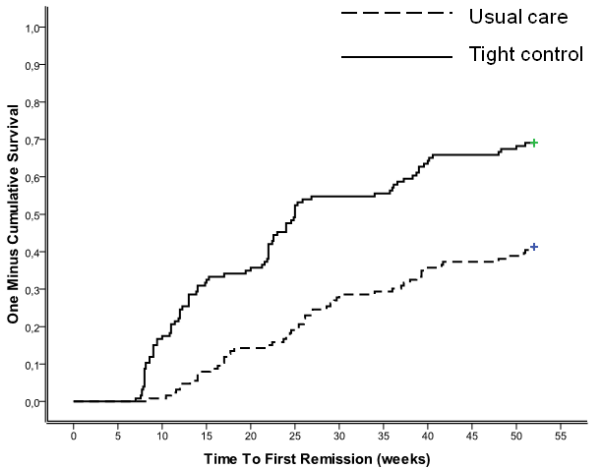

Figure 2. Time to achieve first remission after 1 year of follow-up. Survival curve of time to reach remission (DAS28 <2.6) for tight-control and usual-care groups over 1 year.
DAS28, Disease Activity Score based on 28 joint counts.

Course over time of the DAS28

Figure 3 depicts the course over time of the DAS28 in both groups. It can be seen that the decrease in DAS28 was similar for both groups in the first 12 weeks of treatment, but after 12 weeks the decrease continued in the tight-control group. Also according to the mixed models analysis, the course over time of DAS28 was significantly different between both groups (p<0.0001).

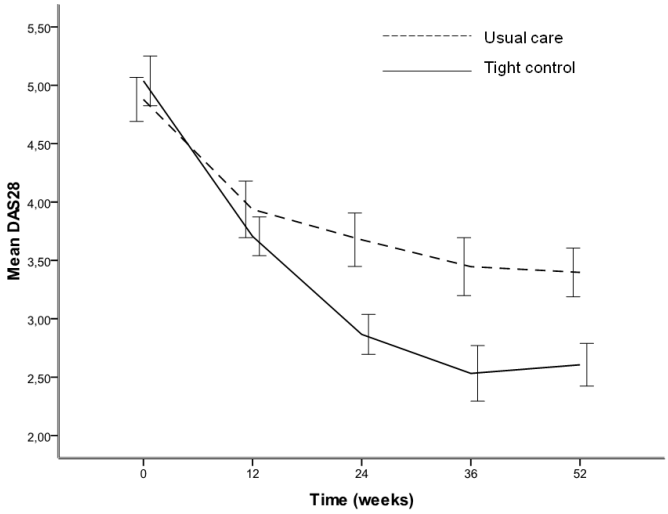

Figure 3. Mean (SEM) decrease of DAS28 in tight-control and usual care groups over 1 year.
DAS28, Disease Activity Score based on 28 joints.

Decrease in DAS28 and core set variables

Table 2 shows the average changes from baseline to 1 year of individual core set variables and the DAS28. In all core set variables, except for the acute phase response (erythrocyte sedimentation rate and C reactive protein), the improvements were significantly larger in the tight-control group.

Table 2. Average change from baseline to 1 year in core set variables.

	Tight control (n = 126)	**Usual care (n = 126)**	***p* Value***
DAS28 (mean (±SD))	-2.5 [1.3]	-1.5 [1.4]	0.000
HAQ score (median (IQR)	-0.5 [-1- -0.2]	-0.3 [-0.8-0]	0.003
Swollen joint count (median (IQR))	-7 [-10--3]	-3 [-8-0]	0.000
Tender joint count (median (IQR))	-4 [-8--1]	-2 [-6-0]	0.000
ESR (median (IQR))	-11 [-28--2]	-12 [-25--1]	0.542
CRP (median (IQR))	-5 [-28-0]	-3 [-21-0]	0.397
VAS pain (mean (SD))	-30 [27]	-16 [28]	0.000
VAS GH (mean (SD))	-32 [28]	-16 [27]	0.000

The negative values indicate improvement from baseline.

IQR, P25-P75.

**p* value for between group comparisons.

CRP, C reactive protein; DAS28, Disease Activity Score based on 28 joint counts; ESR, erythrocyte sedimentation rate; GH, general health; HAQ, Health Assessment Questionnaire; VAS, Visual Analogue Scale.

Medication use

Patients in the tight-control group started with MTX (Table 3). After 1 year, 50% of the patients were still on MTX mono treatment, and 30% received a combination of DMARDs, nearly always MTX and SSZ. After 1 year, 12% of the patients in the tight-control group received anti-TNF, and 9 (7%) patients started adalimumab every week. Intra-articular injections with methylprednisolone were given to 25% of the patients who received one to three injections.

Patients treated according to usual care usually started with MTX or SSZ mono treatment (Table 3). After 1 year of follow-up, most patients were still on DMARD mono treatment; about 19% had switched to another DMARD, and 16% of the patients had two DMARDs. After 1 year, anti-TNF treatment had been given for 6% of the patients. Oral prednisolone was given to 20% of the patients in a median dose of 15 mg/day, and 54% of the patients received one to three intramuscular injections with methylprednisolone 120 mg.

Drug survival and adverse events

In the tight-control group, 120 patients started MTX and 12 (10%) patients stopped MTX again. Nine of them switched to another DMARD, and three patients restarted MTX. Reasons for stopping MTX were toxicity (n=9), patient's wish (n=2) and an unknown reason (n=1).

In the control group, 94 patients started MTX during the year, and 10 (11%) patients stopped again, for toxicity (n=6), inefficacy (n=1) and other reasons (n=3). Of the 44 patients who started SSZ, 22 (50%) stopped using SSZ, usually because of toxicity (n=19).

Table 3. Medication use in tight-control (n=126) and usual-care (n=126) groups.

		Week0		Week 12		Week 24		Week 36		Week 52	
Medication		**UC**	**TC**	**UC**	**TC**	**UC**	**TC**	**UC**	**TC**	**UC**	**TC**
MTX mono		71 [56%]	118 [94%]	75 [60%]	120 [95%]	73 [60%]	66 [52%]	67 [53%]	59 [47%]	66 [52%]	66 [52%]
SSZ mono		44 [35%]	–	34 [27%]	–	32 [25%]	–	30 [24%]	1 [1%]	29 [23%]	1 [1%]
MTX + SSZ		–	–	4 [3%]	–	9 [7%]	48 [38%]	12 [10%]	38 [30%]	12 [10%]	31 [25%]
MTX + anti-TNF		–	–	–	–	2 [2%]	–	6 [5%]	11 [9%]	7 [6%]	14 [11%]
Other DMARD mono		8 [6%]	–	7 [5%]	–	4 [3%]	3 [3%]	5 [5%]	3 [3%]	5 [5%]	3 [3%]
Other DMARD combination		–	–	–	1 [1%]	2 [2%]	4 [3%]	6 [5%]	5 [5%]	7 [6%]	4 [3%]
Other DMARD anti-TNF		–	–	–	–	–	–	–	2 [2%]	–	1 [1%]
No DMARD		3 [4%]	8 [4%]	6 [5%]	5 [4%]	4 [3%]	5 [5%]	–	7 [6%]	–	6 [5%]
Additional	Orally	6 [5%]	0	10 [8%]	25 [20%]	16 [13%]	19 [15%]	15 [12%]	15 [12%]	15 [12%]	15 [12%]
glucocorticosteroids	Intramuscular	19 [15%]	–	54 [43%]	–	26 [21%]	–	21 [17%]	–	18 [14%]	–
	Intra-articular	–	NA	–	NA	–	NA	–	NA	–	NA

TNF, tumour necrosis factor; DMARDs, disease modifying antirheumatic drugs; MTX, methotrexate; NA, not available; SSZ, sulphasalazine; TC, tight control; UC, usual care.

Discussion

According to the results of this study, a tight control treatment strategy aiming for remission leads to more patients being in remission more rapidly than treatment according to usual care in early RA. After 1 year, remission (DAS28<2.6) was reached in 55% of patients in the tight-control group as compared to 30% of patients in the usual-care group. Concordantly, the tight control strategy resulted in a larger decrease of DAS28, more patients having low disease activity, and larger improvements in functional ability and patient assessments of pain and disease activity. The tight control regimen could well be tolerated and did not appear to cause additional toxicity; 88% of the patients still used MTX after 1 year. Tight control performed nearly equally well in patients with shorter (≤18 weeks) and longer symptom duration, but the performance of usual care was much less in patients with longer disease duration.

This quasi-experimental study was performed using daily practice data of two early RA cohorts. The results of this study are in accordance with those from tight control randomised controlled trials Tight Control of Rheumatoid Arthritis (TICORA), Computer Assisted Monitoring of Rheumatoid Arthritis (CAMERA) (12,13). Also, the quasi-experimental study of Goekoop *et al* compared tight control treatment with usual care and showed a better response after 1 year for tight control (14). The results from the current study are valuable, as they contribute to the robustness of the finding that tight control is effective and feasible for the treatment of early RA in daily practice. In this study, it is also pointed out that, in usual care, early treatment (≤18 weeks symptom duration) is more effective than later treatment (>18 weeks) (29). The negative effect of longer symptom duration on outcome could be encountered by using intensive DMARD treatment, as applied in the tight control strategy. But both in ≤18 weeks and in >18 weeks subgroups, tight control was significantly more effective than usual care.

Notably, a beneficial effect on disease activity is reached through medication in the therapeutic regimen, not by measurement and target setting per se. The difference between the two groups in this study was in the strictness of the rules when to prescribe which medication. Therefore, it can be deduced that adding a treatment protocol to the measurement and goal setting is needed to optimise the effects of tight control. The main differences in treatment strategy between the groups were that, in the tight-control group, nearly all patients started with MTX, while MTX start was delayed in the usual care group, and that combination treatment and anti-TNF was more frequently used in the tight-control group.

There also are worries about tight control. Patients would not tolerate the intensivation of MTX (DMARD) treatment and would cycle too quickly through all treatment options. In the tight-control arm of this study, MTX was well tolerated. MTX 1-

year drug survival was 88%, and the proportion of toxicity related drug stops was similar to the usual care group. Moreover, anti-TNF was not much needed, and at 1 year, no patients had moved through the complete treatment algorithm. In the usual-care group, the drug survival of SSZ appeared to be poor, and quite much intramuscular glucocorticosteroids was needed as 'bridge' or 'escape' treatment. The implications of the findings of this study are that aiming for remission is feasible in daily clinical practice and that clinical remission, or rather near-remission, can be our current treatment goal (3,30). In essence, remission should be regarded as the absence of clinical disease activity and absence of progression of joint damage (31,32). Performing tight control places a burden on busy practice. However, the model of tight control in early RA is that many visits and medication changes are performed in the beginning of the disease, with the outlook of reducing the number of visits later. As the name 'tight control' indicates, apparently some degree of vigorousness is needed in bringing tight control to a success in daily clinical practice. Further, tight control with protocolised treatment adjustments contributes to a better disease outcome compared to non-protocolised treatment adjustments (15,17,33). A multitude of treatment strategies have shown to be effective in RA, and there is choice as to which could be used in a treatment protocol (1,8,11,16,34-36).

This study also has its limitations. In this study, DAS28 was used to define remission in early RA. However, patients with a DAS28<2.6 may have residual disease activity, and synovitis may be present in joints not included in the 28 joint count (37). More stringent remission criteria are infrequently met in patients with RA (38). The finding that a DAS28<2.6 can be reached in practice, as we showed, supports the movement to more stringent remission criteria. Another limitation of this study is the follow-up of 1 year. We regard that 1 year is reasonably informative but longer follow-up is needed to get insight into long-term efficacy of tight control, also regarding progression of joint damage. Data on joint damage progression are currently not available. Future research in these cohorts will focus on long-term effects, joint damage progression, safety and performance in patients fulfilling the revised American College of Rheumatology/European League Against Rheumatism classification criteria for RA (19). While as much as 75% of patients were in low disease activity after 1 year, there were still 25% of patients with moderate or high disease activity. This raises two questions for future research: how many patients will attain sustained remission and may reduce medication, and what is an appropriate strategy for patients not able to reach low disease activity?

In conclusion, it was shown that in early RA, a tight-control approach including regular measurement of the DAS28 and protocolised treatment decisions is feasible in

daily practice and that it leads to more rapid DAS28 remission and higher percentages of DAS28 remission after 1 year than usual care treatment.

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References

1. Breedveld FC. Current and future management approaches for rheumatoid arthritis. Arthritis Res 2002;4 Suppl 2:S16-21.
2. Smolen JS, Aletaha D, Machold KP. Therapeutic strategies in early rheumatoid arthritis. Best Pract Res Clin Rheumatol 2005;19:163-77.
3. Combe B, Landewe R, Lukas C, Bolosiu HD, Breedveld F, Dougados M, 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.
4. Lard LR, Visser H, Speyer I, vander Horst-Bruinsma IE, Zwinderman AH, Breedveld FC, et al. Early versus delayed treatment in patients with recent-onset rheumatoid arthritis: comparison of two cohorts who received different treatment strategies. Am J Med. 2001;111:446-51.
5. Nell VP, Machold KP, Eberl G, Stamm TA, Uffmann M, Smolen JS**.** 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.
6. Korpela M, Laasonen L, Hannonen P, Kautiainen H, Leirisalo-Repo M, Hakala M, et al. Retardation of joint damage in patients with early rheumatoid arthritis by initial aggressive treatment with disease-modifying antirheumatic drugs: five-year experience from the FIN-RACo study. Arthritis Rheum. 2004;50:2072-81.
7. Mottonen T, Hannonen P, Leirisalo-Repo M, Nissila M, Kautiainen H, Korpela 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.
8. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJ, Hazes JM, 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.
9. Emery P, Breedveld FC, Hall S, Durez P, Chang DJ, Robertson D, et al. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. Lancet. 2008;372:375-82.
10. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum. 2006;54:26-37.

11. Boers M, Verhoeven AC, Markusse HM, van de Laar MA, Westhovens R, van Denderen JC, et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet. 1997;350:309-18.
12. Grigor C, Capell H, Stirling A, McMahon AD, Lock P, Vallance R, 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.
13. Verstappen SM, Jacobs JW, van der Veen MJ, Heurkens AH, Schenk Y, ter Borg EJ, 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.
14. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Kerstens PJ, Nielen MM, Vos K, van Schaardenburg D, et al. DAS-driven therapy versus routine care in patients with recent-onset active rheumatoid arthritis. Ann Rheum Dis. 2010;69:65-9.
15. Kiely PD, Brown AK, Edwards CJ, O'Reilly DT, Ostor AJ, Quinn M, et al. Contemporary treatment principles for early rheumatoid arthritis: a consensus statement. Rheumatology (Oxford). 2009;48:765-72.
16. Klarenbeek NB, Allaart CF, Kerstens PJ, Huizinga TW, Dijkmans BA**.** The BeSt story: on strategy trials in rheumatoid arthritis. Curr Opin Rheumatol. 2009;21:291-8.
17. Bakker MF, Jacobs JW, Verstappen SM, Bijlsma JW**.** Tight control in the treatment of rheumatoid arthritis: efficacy and feasibility. Ann Rheum Dis. 2007;66 Suppl 3:iii56-60.
18. Schipper LG, van Hulst LT, Grol R, van Riel PL, Hulscher ME, Fransen J**.** 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.
19. Sokka T, Pincus T. Eligibility of patients in routine care for major clinical trials of anti-tumor necrosis factor alpha agents in rheumatoid arthritis. Arthritis Rheum 2003;48:313-8.
20. Zink A, Strangfeld A, Schneider M, Herzer P, Hierse F, Stoyanova-Scholz M, et al. Effectiveness of tumor necrosis factor inhibitors in rheumatoid arthritis in an observational cohort study: comparison of patients according to their eligibility for major randomized clinical trials. Arthritis Rheum. 2006;54:3399-407.
21. Kuper I, Hoekstra M, ten Klooster P et al. Remission can be achieved in 50% of early rheumatoid arthritis patients after 25 weeks in daily clinical practice. Ann Rheum Dis 2008;67(Suppl II):48.

22. Welsing PM, van Riel PL. The Nijmegen inception cohort of early rheumatoid arthritis. J Rheumatol 2004;69:S14-S21.
23. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988;31:315-24.
24. Furst DE, Breedveld FC, Kalden JR, Smolen JS, Burmester GR, Sieper J, et al. Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2007. Ann Rheum Dis. 2007;66 Suppl 3:iii2-22.
25. Schipper LG, Hoekstra M, Vliet Vlieland TP, Jansen TL, Lems WF, van Riel PL. [Practice guideline 'Diagnosis and treatment of rheumatoid arthritis']. Ned Tijdschr Geneesk 2009;153:A944.
26. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL**.** 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.
27. Zandbelt MM, Welsing PM, van Gestel AM, van Riel PL**.** Health Assessment Questionnaire modifications: is standardisation needed? Ann Rheum Dis. 2001;60:841-5.
28. van Gestel AM, Haagsma CJ, van Riel PL. Validation of rheumatoid arthritis improvement criteria that include simplified joint counts. Arthritis Rheum 1998;41:1845-50.
29. Söderlin MK, Bergman S. Absent “Window of Opportunity” in Smokers with Short Disease Duration. Data from BARFOT, a Multicenter Study of Early Rheumatoid Arthritis. J Rheumatol 2011;38:2160-8.
30. Smolen JS, Aletaha D. What should be our treatment goal in rheumatoid arthritis today? Clin Exp Rheumatol 2006;24(Suppl 43):S7-S13.
31. Molenaar ET, Voskuyl AE, Dinant HJ, Bezemer PD, Boers M, Dijkmans BA**.** Progression of radiologic damage in patients with rheumatoid arthritis in clinical remission. Arthritis Rheum. 2004;50:36-42.
32. 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(6 Suppl 43):S-22-8.
33. Sokka T, Makinen H. Drug management of early rheumatoid arthritis - 2008. Best Pract Res Clin Rheumatol 2009;23:93-102.
34. O'Dell JR. Therapeutic strategies for rheumatoid arthritis. N Engl J Med 2004;350:2591-602.

35. Donahue KE, Gartlehner G, Jonas DE, Lux LJ, Thieda P, Jonas BL, et al. Systematic review: comparative effectiveness and harms of disease-modifying medications for rheumatoid arthritis. Ann Intern Med. 2008;148:124-34.
36. van der Kooij SM, Allaart CF, Dijkmans BA, Breedveld FC**.** Innovative treatment strategies for patients with rheumatoid arthritis. Curr Opin Rheumatol. 2008;20:287-94.
37. Makinen H, Kautiainen H, Hannonen P, Sokka T. Is DAS28 an appropriate tool to assess remission in rheumatoid arthritis? Ann Rheum Dis. 2005;64:1410-3.
38. Landewe R, van der Heijde D, van der Linden S, Boers M. 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.

Chapter 4 |

Sustained beneficial effects of a protocolized treat-to-target strategy in very early rheumatoid arthritis: three year results of the DREAM remission induction cohort

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Abstract

Objective. Treatment to target (T2T) leads to improved clinical outcomes in early rheumatoid arthritis (RA). The question is whether these results sustain in the long-term. The objective was to investigate the three year results of a protocolized T2T strategy in daily clinical practice.

Methods. In the Dutch Rheumatoid Arthritis Monitoring remission induction cohort, patients newly diagnosed with RA were treated according to a T2T strategy aiming at remission (Disease Activity Score in 28 joints (DAS28) < 2.6). Patients were treated with methotrexate, followed by the addition of sulfasalazine, and exchange of sulfasalazine with anti-tumor necrosis factor α agents in case of failure. Primary outcomes were disease activity, Health Assessment Questionnaire (HAQ) score, SF-36 physical and mental component summary (PCS and MCS, respectively) scores, and the Sharp/van der Heijde (SHS) score after three years. Secondary outcomes were sustained DAS28 remission (≥ six months) and remission according to the provisional American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) definition.

Results. After three years (n=342), 61.7% of patients were in DAS28 remission and 25.3% met the provisional ACR/EULAR definition of remission. Sustained remission was experienced by 70.5%, which in the majority was achieved with conventional disease-modifying antirheumatic drugs only. The median (interquartile range) scores were as follows; HAQ, 0.4 (0.0-1.0); PCS, 45.0 (38.4-53.2); MCS, 53.1 (43.2-60.8); and total SHS, 6.0 (3.0-13.0).

Conclusion. In very early RA, T2T leads to high (sustained) remission rates, improved physical function and health-related quality of life, and limited radiographic damage after three years in daily clinical practice.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease which can have a major impact on the patient's physical and psychological health. When insufficiently treated, RA may lead to serious radiographic damage, functional disability (1-3), and reduced quality of life (4). The main therapeutic goal in RA is to suppress disease activity as early in the disease process as possible, thereby preferably achieving (sustained) remission, in order to prevent radiographic damage and disability (5). Indeed, remission is associated with a lower chance of deterioration of radiographic progression and function in the long-term compared with not achieving a state of remission (6).

Intensified treatment including biologic agents has proven to be effective in achieving remission in patients with recent-onset RA (7). Clinical trials, e.g. the Behandel Strategieën (BeSt) study (8) and Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA) study (9), have demonstrated that intensive therapy including combination therapy and biologics or corticosteroids results in more beneficial clinical outcomes than initial monotherapy with disease-modifying antirheumatic drugs (DMARDs).

Furthermore, treatment to target (T2T) is considered an important concept in the induction of remission in the treatment of RA (10). T2T entails 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 or remission. The Dutch Rheumatoid Arthritis Monitoring (DREAM) remission induction cohort demonstrated that remission is a realistic goal in daily clinical practice with the application of a T2T strategy aiming at remission according to the Disease Activity Score in 28 joints (DAS28) (11), with early and intensive treatment leading to high remission rates (12) and limited radiographic progression after one year of follow-up (13). The question is whether these beneficial results sustain in the long-term. Until now, data on the long-term outcomes of T2T in daily clinical practice are scarce.

The aim of the present study was to investigate the three year effects of the implementation of a protocolized T2T strategy in the treatment of very early RA patients with respect to the achievement of (sustained) remission, radiographic progression, physical function, and health-related quality of life.

Patients and methods

Patients

Between January 2006 and March 2012, newly diagnosed RA patients were invited to participate in the DREAM remission induction cohort and data collection is still ongoing. Patients with a clinical diagnosis of RA (made at the discretion of the attending rheumatologist) were included who were at least 18 years of age, had a symptom duration (defined as time from the first reported symptom to the diagnosis of RA) of one year or less, had a DAS28 ≥ 2.6 and did not use DMARDs and/or prednisolone before.

The rheumatology clinics of 6 hospitals in The Netherlands collaborated in this study. Data collection for this cohort is still ongoing. This observational study on data from protocol-based daily clinical practice was approved by the hospitals' ethics committees Patients were fully informed, and informed consent was obtained.

Treatment

Patients were treated according to a T2T strategy including 4-12 weekly follow-up visits and protocolized treatment adjustments aiming at remission (DAS28 < 2.6). Therapy consisted of initial methotrexate monotherapy (MTX), followed by the addition of sulfasalazine (SSZ) and exchange of SSZ by anti-tumor necrosis factor (TNF) α agents in case of failure. If the target of DAS28 < 2.6 was met, medication was not changed. In case of sustained remission (≥ six months), medication was gradually reduced and eventually discontinued. In case of a disease flare (DAS28 ≥ 2.6), the most recently effective medication or medication dosage was restarted and treatment could be subsequently intensified. In individual patients with contraindications for specific medication, deviations from the protocol were allowed. Concomitant treatment with nonsteroidal anti-inflammatory drugs, prednisolone at a dosage of ≤ 10 mg/day and intra-articular corticosteroid injections were allowed at the discretion of the attending rheumatologist. Further details of the study protocol were reported elsewhere (13).

Assessments

The following variables were collected at baseline: age, sex, symptom duration, fulfillment of the American College of Rheumatology (ACR) 1987 criteria for the classification of RA (14), rheumatoid factor (RF) positivity, and anti-cyclic citrullinated peptide antibody (anti-CCP) positivity. Assessments at baseline and at every follow-up visit (week 8, 12, 20, 24, 36 and 52, and every 3 months thereafter) included the DAS28 (including the 28 tender joint count (TJC28), 28 swollen joint count (SJC28), erythrocyte sedimentation rate (ESR), and patient rating for general health on a 100 mm visual analog scale (VAS; 0=best and

100=worst)), C-reactive protein (CRP), and patient rating for pain on a 100 mm VAS. The DAS28 was assessed by trained rheumatology nurses.

The Dutch version of the Health Assessment Questionnaire (HAQ) (15,16) and the 36-item Short Form Health Survey (SF-36) (17) were administered every three months. The HAQ disability index ranges from 0 to 3, with higher scores indicating more disability. The SF-36 generates a physical and mental component summary (PCS and MCS, respectively) score, ranging from 0 to 100, with higher scores indicating better health.

Radiographs of the hands and feet were obtained at baseline, after six and twelve months, and then annually. Radiographs were evaluated in chronologic order by two pairs of observers (MV and HHK/HJBM/KWD), according to the original methodology developed and published as "modified Sharp/van der Heijde method" (18), and a consensus score was obtained. A patient was classified as having erosive disease if the erosion score was ≥ 1. An expert panel judged the minimal clinically important difference in the total Sharp/van der Heijde score (SHS) at an increase of ≥ 5 (19).

Study outcomes

The primary outcomes after three years of follow-up were disease activity according to the DAS28, the median scores of the HAQ and SF-36 (PCS and MCS), and radiographic outcome according to the SHS. Secondary outcomes included sustained DAS28 remission, time to achieve as well as the duration of sustained DAS28 remission, the number of disease flares, and remission according to the provisional ACR/European League Against Rheumatism (EULAR) definition of remission in RA (20).

Sustained remission was defined as a DAS28 < 2.6 during ≥ six consecutive months. Sustained remission could be classified as drug-free or biologic-free when remission was sustained (≥ six consecutive months) without any antirheumatic drugs or after withdrawal of anti-TNF therapy, respectively. The Boolean-based definition of the provisional ACR/EULAR definition of remission in RA required a TJC28 ≤ 1, SJC28 ≤ 1, CRP ≤ 1 mg/dl and patient global assessment (PGA) ≤ 1 (on a 0-10 scale) (20). In a previous study, we demonstrated that many patients did not meet the PGA criterion despite a good clinical disease state (21). Therefore, we also assessed the provisional ACR/EULAR definition of remission without the PGA criterion.

Statistical analyses

Since we were interested in the three year outcomes, only patients enrolled in the cohort between January 2006 and March 2009 were selected for the present study.

In case of missing values of the DAS28, HAQ, SF-36 and SHS scores, imputation using the trapezoid method was used, conditional on the data being missing at random.

A completers analysis as well as an intention-to-treat analysis was performed on the primary study variables after three years of follow-up. For the completers analysis, we used only the data of patients in which data on the three years follow-up visit were available. In the intention-to-treat analysis, the last observation was carried forward, i.e. if data was missing at the three year follow-up visit, then the data from the most proximal prior visit was used.

Kaplan-Meier survival analysis was performed to assess time to achieve sustained DAS28 remission.

P values less than 0.05 were considered significant. Statistical analyses were performed using SPSS version 18.0 software.

Results

Baseline characteristics

A total of 409 patients were eligible for the present study. Table 1 shows the baseline characteristics of the patients. The mean (standard deviation (SD)) age at baseline was 58.4 (14.0) years and 62.1% (254/409) of the patients were female. Patients were included at the moment of diagnosis and, therefore, disease duration was, per definition, 0 weeks. The patients had on average a high level of disease activity as shown by the mean (SD) DAS28 of 5.0 (1.1). Erosive disease was already present in 45.8% (169/369) of the patients and the median (interquartile range (IQR)) total SHS was 2.0 (0.0-5.0).

Three year follow-up data were available for 342 (83.6%) patients. In total, 67 patients were lost to follow-up or did not have three years data for various reasons: death (n=9), moving out of the area (n=14), comorbidity (n=7), other diagnosis (n=1), patient wish (n=22), other (n=5), and no three year follow-up visit yet (n=9). These patients were older (mean (SD) 64.2 (13.3) vs. 57.3 (13.9), $p < 0.001$), had a higher ESR (median (IQR) 36.0 (24.0-53.0) vs. 28.0 (16.0-42.0), $p=0.007$) and CRP (median (IQR) 24.0 (9.3-39.0) vs. 13.0 (5.0-31.3), $p=0.03$), and were more often anti-CCP positive (56.1% vs. 39.2%, $p=0.017$), but they did not differ significantly from the completers with respect to the distribution of sex and other clinical variables at baseline.

Both an analysis on the completers (n=342) and an intention-to-treat analysis on the total cohort (n=409) were performed. The results of both analyses did not differ, and therefore, we present only the results of the completers analysis.

Table 1. Baseline characteristics of the patients (n=409).

Female sex, n (%)	254 (62.1)
Age, mean ± SD years	58.4 ± 14.0
Symptom duration, weeks	14.0 (8.0-26.0)
Fulfillment of ACR 1987 criteria for RA, n (%)	334/398 (83.9)
RF positive, n (%)	246/406 (60.6)
Anti-CCP positive, n (%)	219/376 (58.2)
Erosive disease, n (%)	169/369 (45.8)
Total SHS	2.0 (0.0-5.0)
ESR, mm/hour	30.0 (17.0-44.0)
CRP, mg/liter	15.0 (5.0-34.0)
No. of tender joints (28 assessed)	5.0 (2.0-9.0)
No. of swollen joints (28 assessed)	8.0 (5.0-12.0)
DAS28, mean ± SD	5.0 ± 1.1
Patient's assessment of pain (0-100 VAS)	50.0 (36.0-70.0)
Patient's assessment of general health (0-100 VAS)	50.0 (37.0-70.0)
HAQ score	1.0 (0.5-1.4)
SF-36 PCS score	35.6 (29.9-42.4)
SF-36 MCS score	48.0 (38.5-58.2)

Values are the median (interquartile range) unless otherwise noted.

ACR, American College of Rheumatology; anti-CCP, anti-cyclic citrullinated peptide; CRP, C-reactive protein; DAS28, Disease Activity Score in 28 joints; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; MCS, mental component summary; PCS, physical component summary; RF, rheumatoid factor; SD, standard deviation; SF-36, Short-Form 36 health survey; SHS, Sharp/van der Heijde score; VAS, visual analog scale.

Disease activity

After three years, the mean (SD) DAS28 was decreased to 2.4 (1.0). Figure 1 shows the course of the DAS28 over time. The largest improvement in DAS28 was observed in the first six months of treatment, with a mean (SD) change in DAS28 of -2.1 (1.4) points (p < 0.001).

Table 2 presents the remission percentages at four time points during the study. After three years, 61.7% (221/342) of the patients were in DAS28 remission. The provisional ACR/EULAR remission definition was met in 25.3% (74/293) and the adapted ACR/EULAR remission definition was met in 60.9% (179/294). The percentages of DAS28 remission and remission according to the adapted ACR/EULAR remission definition increased significantly during the first year (all p < 0.01). The one year remission percentages remained consistent over follow-up, except for the percentage of adapted ACR/EULAR remission which increased significantly from one to two years (p < 0.01).

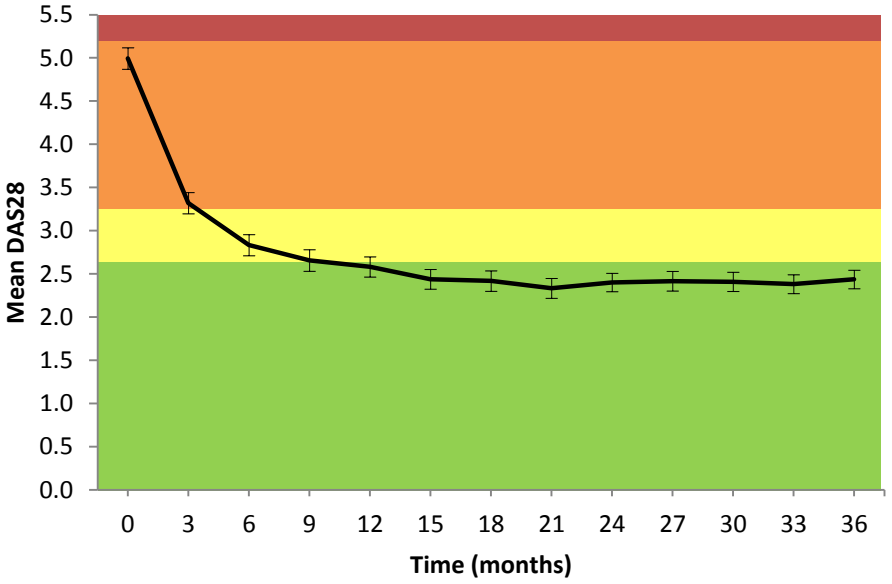

Figure 1. The mean (standard error of the mean) of the Disease Activity Score in 28 joints (DAS28) over three years of follow-up.
Background coloring represents the levels of disease activity: green, remission (DAS28 < 2.6); yellow, low (2.6 ≤ DAS28 ≤ 3.2); orange, moderate (3.2 < DAS28 ≤ 5.1); red, high (DAS28 > 5.1).

Table 2. Levels of disease activity over three years of follow-up (n=342).

	6 months	**1 year**	**2 years**	**3 years**
DAS28 level				
Remission (DAS28 < 2.6)	160 (46.8)	198 (57.9)	217 (63.5)	211 (61.7)
Low (2.6 ≤ DAS28 ≤ 3.2)	67 (19.6)	49 (14.3)	64 (18.7)	66 (19.3)
Moderate (3.2 < DAS28 ≤ 5.1)	101 (29.5)	86 (25.1)	54 (15.8)	57 (16.7)
High (DAS28 > 5.1)	14 (4.1)	9 (2.6)	7 (2.0)	8 (2.3)
Provisional ACR/EULAR remission	57/335 (17.0)	67/318 (21.1)	79/309 (25.6)	74/293 (25.3)
Adapted provisional ACR/EULAR remission†	116/334 (34.7)	157/319 (49.2)	189/307 (61.6)	179/294 (60.9)

Values are the number (percentage).
Provisional American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) remission could not be evaluated in all patients due to missing values for C-reactive protein and/or patient global assessment (PGA).
DAS28, Disease Activity Score in 28 joints.
† The provisional ACR/EULAR definition of remission without the PGA criterion.

Sustained remission

In 70.5% (241/342) of the patients, sustained DAS28 remission (≥ six months) was observed at least once during the first three years of follow-up, of which in 74.7% (180/241) remission was sustained for more than one year. At the three year follow-up visit, sustained remission was present in 42.7% (146/342) of patients.

The Kaplan-Meier estimate of the median (IQR) time to the achievement of the first sustained remission was 1.2 (1.0-1.4) years. Obviously, not all patients reaching remission stayed in remission. The median (IQR) duration of the first sustained remission was 1.5 (0.9-2.3) years. In 51.0% (123/241) of the patients who experienced sustained remission, the disease did not flare. Almost a quarter (28/118) of the patients who experienced a disease flare experienced a second sustained remission.

In the majority of cases (85.5%, 206/241) sustained remission was achieved with conventional DMARDs only. Sustained remission was induced by adjuvant therapy with anti-TNF agents in 12.0% (29/241) and in 2.5% (6/241) sustained remission was observed without antirheumatic medication. After achieving sustained remission, medication was tapered in 65.6% (158/241) of patients, discontinued in 18.7% (45/241), unchanged in 9.1% (22/241), and switched to another antirheumatic drug in 6.6% (16/241) because of other reasons. Of the 29 patients who achieved sustained remission on an adjuvant anti-TNF agent, biologic-free sustained remission was achieved in 24.1% (7/29) of the patients. Sustained drug-free remission was observed in 14.9% (51/342).

Physical function

At three years, the HAQ score was available for 286 (83.6%) patients. Figure 2A presents the box plots of the HAQ scores during follow-up. At three years, the median (IQR) HAQ score was 0.4 (0.0-1.0). The HAQ strongly improved during the first six months of treatment and this improvement was maintained during follow-up.

Health-related quality of life

Three year data on the SF-36 were available for 284 (83.0%) patients. Figure 2B and 2C present the box plots of the SF-36 PCS and MCS scores during follow-up. The median (IQR) scores of the PCS and MCS after three years were 45.0 (38.4-53.2) and 53.1 (43.2-60.8), respectively. After six months of follow-up, significant improvements in the PCS and MCS were observed, and the SF-36 scores remained stable hereafter.

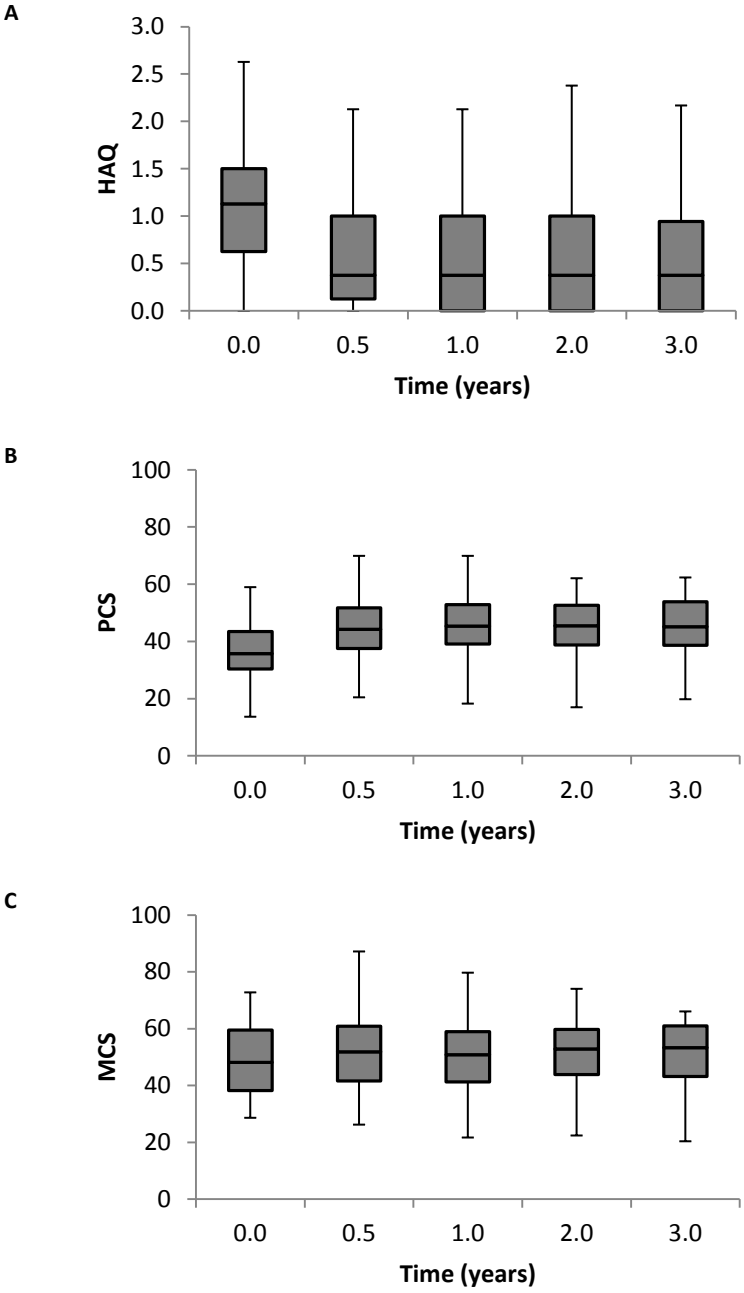

Figure 2. Box plots of A) the Health Assessment Questionnaire (HAQ), B) Short-Form 36 health survey physical component summary (PCS) and C) mental component summary (MCS) over three years of follow-up.

Radiographic progression

Three year radiographic data were available for 325 (95.0%) of the patients. Unavailability of three years' radiographs was due to various reasons.

Table 3 presents the radiographic outcomes at four time points during three years of follow-up. After three years, 76.3% (248/325) of the patients had erosive disease. The percentage of patients with erosive disease significantly increased between baseline and 1 year of follow-up (44.9% vs. 70.5%, $p < 0.001$). Figure 3 presents the course of the SHS over time. From baseline to three years, the median (IQR) annual total SHS progression rates were as follows: 2.0 (1.0-4.0), 1.0 (0.0-2.0), and 0.0 (0.0-2.0), respectively. After three years, the median (IQR) total SHS was 6.0 (3.0-13.0) and clinically relevant progression was observed in 43.4% (141/325) of the patients.

Table 3. Radiographic outcomes over three years of follow-up (n=325).

	6 months	1 year	2 years	3 years
Erosive disease, n (%)	204 (62.8)	229 (70.5)	242 (74.5)	248 (76.3)
Erosion score	1.0 (0.0-3.0)	2.0 (0.0-4.0)	2.0 (0.0-5.0)	2.0 (1.0-6.0)
Joint space narrowing score	2.0 (0.0-4.0)	2.0 (0.0-5.0)	2.0 (1.0-6.0)	3.0 (1.0-7.0)
Total SHS	3.0 (1.0-7.0)	4.0 (2.0-9.0)	5.0 (2.0-11.0)	6.0 (3.0-13.0)

Values are the median (interquartile range, IQR) unless otherwise noted.
SHS, Sharp/van der Heijde score.

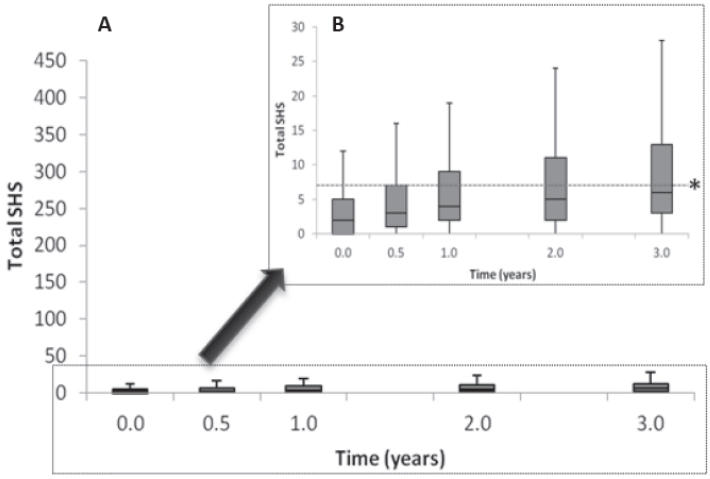

Figure 3. Box plots of the Sharp/van der Heijde score (SHS) over three years of follow-up, A) represented on the full range of the score (0-448) and B) zoomed into the range of the observed scores.

* The dotted line (SHS = 7) represents the clinically important difference in SHS (i.e. 5) from the baseline median SHS score (i.e. 2).

Medication

In the remission group (n=211), the actual medication use at the three year follow-up visit was as follows: 43.1% (91/211) of the patients were being treated with MTX monotherapy, 6.2% (13/211) received MTX and SSZ, 9.0% (19/211) received other DMARD medication, 16.6% (35/211) (received MTX in combination with a biologic agent (12.3% adalimumab, 3.8% etanercept, and 0.5% infliximab), and 25.1% (53/211) were medication-free, Low-dose prednisolone (≤ 10 mg/day) was added to the medication in 6.2% (13/211).

In the non-remission group (n=131), the actual medication use at the three year follow-up visit was as follows: 43.5% (57/131) of the patients received MTX monotherapy, 5.3% (7/131) received MTX with SSZ, 16.8% (22/131) were given other DMARD therapy, 20.6% (27/131) received MTX with a biologic agent (12.2% adalimumab, 4.6% etanercept, and 3.8% infliximab), and 13.8% (18/131) were medication-free. Prednisolone was used in 13.0% (17/131) of patients.

Discussion

This long-term follow-up study demonstrated that the early beneficial outcomes of a protocolized T2T strategy aiming at remission in very early RA in daily clinical practice are sustained over three years. T2T resulted in low disease activity, improvement of physical function and health-related quality of life, and a favorable radiographic outcome after three years of follow-up.

High remission percentages were observed during follow-up and remission was sustained (≥ six months) in the majority of patients (71%). Remission was maintained for more than one year in 53% of patients. These results are notable since previous studies have suggested that sustained remission is uncommon in daily clinical practice (22-25). In the majority of our patients, sustained remission was achieved with conventional DMARDs (monotherapy or combination therapy). This is in line with other studies showing that optimal use of MTX early in the disease course leads to considerable improvements in disease activity (9,26). Moreover, a shorter time to remission has shown to be related to sustainability of remission, supporting the importance of early intervention with effective therapy to achieve early remission (27). In spite of achieving sustained remission, it is important to continue to frequently and strictly monitor disease activity as a proportion of the patients may experience a disease flare. In line with the favorable results on disease activity, physical function (i.e. HAQ) and health-related quality of life (i.e. SF-36) demonstrated significant and clinically meaningful improvements over the three year follow-up.

Although the baseline radiological damage scores were low, 76% of patients proved to have erosive disease during observation. However, the total SHS score and the

progression in SHS were extremely low after three years of follow-up. It must be mentioned that we used the original methodology for the SHS score, so all radiographs of one patient are evaluated in chronologic order and thus only progression can be scored. This is in contrast with some recent radiological studies suggesting healing of erosions (28-30). In our cohort we have observed the same phenomena in individuals but due to the original SHS methodology this cannot be seen in the data.

Among the major strengths of this study are the large size of the cohort, the long follow-up period and the fact that it concerns prospectively observed real-life data of newly diagnosed RA patients in clinics that implemented T2T in combination with protocolized treatment. Therefore, the results of this study in daily clinical practice can be generalized to the general RA population. Data collection of the cohort is still ongoing, which is critical for examining whether sustained drug-free remission is an achievable goal in daily clinical practice.

This study has some limitations. First, the target of this treatment strategy was remission according to the DAS28, which has some shortcomings. Although the DAS28 score requires a complex calculation and its remission cut-off point has been debated (31-33), it is widely implemented, especially in Europe. Moreover, we have shown that all remission definitions are strongly related. In our opinion our data underline the importance of treating RA to the target of remission, where remission can be assessed by any of the available definitions. Second, it is inevitable that a part of the patients become lost to follow-up in cohort studies. Therefore, a completers analysis as well as an intention-to-treat analysis was performed. Since both analyses led to comparable results, the fact that some patients were lost to follow-up did not affect our outcomes. Third, our results reflect the effects of only one medication strategy; no comparator was included. Recently, we compared the short-term results of our cohort with a comparable cohort in which usual care treatment was applied, demonstrating that T2T had superiority (12).

T2T has emerged as a new paradigm for the treatment of early RA. However, T2T has not been fully implemented in all rheumatology clinics yet. The DREAM remission induction cohort demonstrated that a DAS28-driven T2T strategy is feasible in early RA daily clinical practice, and herewith achieving and sustaining remission becomes a realistic treatment goal.

In conclusion, the present study showed that in daily clinical practice, a protocolized T2T strategy for very early RA leads to low disease activity and high (sustained) remission rates, improved physical function, better health-related quality of life and limited radiographic damage, which sustain over three years.

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References

1. Drossaers-Bakker KW, de Buck M, van Zeben D, Zwinderman AH, Breedveld FC, Hazes JM**.** Long-term course and outcome of functional capacity in rheumatoid arthritis: the effect of disease activity and radiologic damage over time. Arthritis Rheum. 1999;42:1854-60.
2. Welsing PM, van Gestel AM, Swinkels HL, Kiemeney LA, van Riel PL**.** The relationship between disease activity, joint destruction, and functional capacity over the course of rheumatoid arthritis. Arthritis Rheum. 2001;44:2009-17.
3. Scott DL, Smith C, Kingsley G**.** Joint damage and disability in rheumatoid arthritis: an updated systematic review. Clin Exp Rheumatol. 2003;21(5 Suppl 31):S20-7.
4. Kingsley G, Scott IC, Scott DL**.** Quality of life and the outcome of established rheumatoid arthritis. Best Pract Res Clin Rheumatol. 2011;25:585-606.
5. Smolen JS, Landewe R, Breedveld FC, Dougados M, Emery P, Gaujoux-Viala C, 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.
6. van Tuyl LH, Felson DT, Wells G, Smolen J, Zhang B, Boers M**.** Evidence for predictive validity of remission on long-term outcome in rheumatoid arthritis: a systematic review. Arthritis Care Res (Hoboken). 2010;62:108-17.
7. Scott DL**.** Biologics-based therapy for the treatment of rheumatoid arthritis. Clin Pharmacol Ther. 2012;91:30-43.
8. van der Kooij SM, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Guler-Yuksel M, Zwinderman AH, Kerstens PJ, et al. Drug-free remission, functioning and radiographic damage after 4 years of response-driven treatment in patients with recent-onset rheumatoid arthritis. Ann Rheum Dis. 2009;68:914-21.
9. Verstappen SM, Jacobs JW, van der Veen MJ, Heurkens AH, Schenk Y, ter Borg EJ, 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.
10. Smolen JS, Aletaha D, Bijlsma JW, Breedveld FC, Boumpas D, Burmester G, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis. 2010;69:631-7.
11. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL**.** 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.

12. Schipper LG, Vermeer M, Kuper HH, Hoekstra MO, Haagsma CJ, Broeder AA, et al. A tight control treatment strategy aiming for remission in early rheumatoid arthritis is more effective than usual care treatment in daily clinical practice: a study of two cohorts in the Dutch Rheumatoid Arthritis Monitoring registry. Ann Rheum Dis. 2012;71:845-50.
13. Vermeer M, Kuper HH, Hoekstra M, Haagsma CJ, Posthumus MD, Brus HL, et al. Implementation of a treat-to-target strategy in very early rheumatoid arthritis: results of the Dutch Rheumatoid Arthritis Monitoring remission induction cohort study. Arthritis Rheum. 2011;63:2865-72.
14. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988;31:315-24.
15. Fries JF, Spitz P, Kraines RG, Holman HR**.** Measurement of patient outcome in arthritis. Arthritis Rheum. 1980;23:137-45.
16. Siegert CE, Vleming LJ, Vandenbroucke JP, Cats A**.** Measurement of disability in Dutch rheumatoid arthritis patients. Clin Rheumatol. 1984;3:305-9.
17. Ware JE, Jr., Sherbourne CD**.** The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30:473-83.
18. van der Heijde D**.** How to read radiographs according to the Sharp/van der Heijde method. J Rheumatol. 2000;27:261-3.
19. Bruynesteyn K, van der Heijde D, Boers M, Saudan A, Peloso P, Paulus H, et al. Determination of the minimal clinically important difference in rheumatoid arthritis joint damage of the Sharp/van der Heijde and Larsen/Scott scoring methods by clinical experts and comparison with the smallest detectable difference. Arthritis Rheum. 2002;46:913-20.
20. Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LH, Funovits J, et al. American college of rheumatology/european league against rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Ann Rheum Dis. 2011;70:404-13.
21. Vermeer M, Kuper HH, van der Bijl AE, Baan H, Posthumus MD, Brus HL, et al. The provisional ACR/EULAR definition of remission in RA: a comment on the patient global assessment criterion. Rheumatology (Oxford). 2012;51:1076-80.
22. Mierau M, Schoels M, Gonda G, Fuchs J, Aletaha D, Smolen JS**.** Assessing remission in clinical practice. Rheumatology (Oxford). 2007;46:975-9.
23. Prince FH, Bykerk VP, Shadick NA, Lu B, Cui J, Frits M, et al. Sustained rheumatoid arthritis remission is uncommon in clinical practice. Arthritis Res Ther. 2012;14:R68.

24. Jayakumar K, Norton S, Dixey J, James D, Gough A, Williams P, et al. Sustained clinical remission in rheumatoid arthritis: prevalence and prognostic factors in an inception cohort of patients treated with conventional DMARDS. Rheumatology (Oxford). 2012;51:169-75.
25. Aletaha D. Nothing lasts forever - a critical look at sustained remission. Arthritis Res Ther. 2012;14:116.
26. Grigor C, Capell H, Stirling A, McMahon AD, Lock P, Vallance R, 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.
27. Schipper LG, Fransen J, den Broeder AA, Van Riel PL. Time to achieve remission determines time to be in remission. Arthritis Res Ther. 2010;12:R97.
28. Menninger H, Meixner C, Sondgen W. Progression and repair in radiographs of hands and forefeet in early rheumatoid arthritis. J Rheumatol. 1995;22:1048-54.
29. Sharp JT, Van Der Heijde D, Boers M, Boonen A, Bruynesteyn K, Emery P, et al. Repair of erosions in rheumatoid arthritis does occur. Results from 2 studies by the OMERACT Subcommittee on Healing of Erosions. J Rheumatol. 2003;30:1102-7.
30. Rau R. Is remission in rheumatoid arthritis associated with radiographic healing? Clin Exp Rheumatol. 2006;24(6 Suppl 43):S-41-4.
31. Landewe R, van der Heijde D, van der Linden S, Boers M. 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.
32. Gaujoux-Viala C, Mouterde G, Baillet A, Claudepierre P, Fautrel B, Le Loet X, et al. Evaluating disease activity in rheumatoid arthritis: which composite index is best? A systematic literature analysis of studies comparing the psychometric properties of the DAS, DAS28, SDAI and CDAI. Joint Bone Spine. 2012;79:149-55.
33. Bakker MF, Jacobs JW, Kruize AA, van der Veen MJ, van Booma-Frankfort C, Vreugdenhil SA, et al. Misclassification of disease activity when assessing individual patients with early rheumatoid arthritis using disease activity indices that do not include joints of feet. Ann Rheum Dis. 2012;71:830-5.

Chapter 5 |

Adherence to a treat-to-target strategy in early rheumatoid arthritis: results of the DREAM remission induction cohort

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Abstract

Introduction. Clinical trials have demonstrated that treatment-to-target (T2T) is effective in achieving remission in early rheumatoid arthritis (RA). However, the concept of T2T has not been fully implemented yet and the question is whether a T2T strategy is feasible in daily clinical practice. The objective of the study was to evaluate the adherence to a T2T strategy aiming at remission (Disease Activity Score in 28 joints (DAS28) < 2.6) in early RA in daily practice. The recommendations regarding T2T included regular assessment of the DAS28 and an advice regarding DAS28-driven treatment adjustments.

Methods. A medical chart review was performed among a random sample of 100 RA patients of the DREAM remission induction cohort. At all scheduled visits, it was determined whether the clinical decisions were compliant to the T2T recommendations.

Results. The 100 patients contributed to a total of 1115 visits. The DAS28 was available in 97.9% (1092/1115) of the visits, of which the DAS28 was assessed at a frequency of at least every three months in 88.3% (964/1092). Adherence to the treatment advice was observed in 69.3% (757/1092) of the visits. In case of non-adherence when remission was present (19.5%, 108/553), most frequently medication was tapered or discontinued when it should have been continued (7.2%, 40/553) or treatment was continued when it should have been tapered or discontinued (6.2%, 34/553). In case of non-adherence when remission was absent (42.1%, 227/539), most frequently medication was not intensified when an intensification step should have been taken (34.9%, 188/539). The main reason for non-adherence was discordance between disease activity status according to the rheumatologist and DAS28.

Conclusion. The recommendations regarding T2T were successfully implemented and high adherence was observed. This demonstrates that a T2T strategy is feasible in RA in daily clinical practice.

Introduction

New insights into the treatment of rheumatoid arthritis (RA) have led to better care for RA patients, thereby strongly improving outcome (1,2). Herewith, clinical remission has become the ultimate therapeutic goal in RA (3). Several studies have demonstrated that a treatment approach including tight control of disease activity is more effective in lowering disease activity and, ultimately, reaching remission, compared with usual care (4-8). The major keystones of such a treat-to-target (T2T) strategy are: 1) regular assessment of the disease activity using a validated outcome measure, 2) subsequent adjustments of treatment in case of persistent disease activity, preferably following a medication protocol where therapeutic consequences are predefined (9), and 3) aiming at a predefined target.

Current recommendations and guidelines on the management of RA address the importance of treating RA to a target of remission or low disease activity (3,10). In this context, the European League Against Rheumatism (EULAR) has formulated a set of ten international recommendations on how to achieve optimal outcomes of RA by providing guidance for T2T (11). Although the rheumatology community worldwide endorses the importance of T2T (12), a lack of compliance with this issue is presumed in daily clinical practice. It is assumed that disease activity is not consistently measured by validated measures and medication is often not intensified or changed when disease is active in the routine care setting (6,13-15).

The implementation of guidelines and the translation of beneficial results of clinical trials to daily clinical practice is considered to be difficult (16-19). The question is whether a T2T strategy including protocolized treatment adjustments will be feasible in a real-life setting, which is characterized by a more heterogeneous patient population (20), variation in prescription behavior of specialists (19,21), and restriction of time, costs and resources.

In 2006, six of the Dutch Rheumatoid Arthritis Monitoring (DREAM) consortium hospitals implemented a T2T strategy in the so-called DREAM remission induction cohort. Four of these six hospitals successfully implemented the strategy and included at least 20 patients. Since the day of diagnosis, very early RA patients were treated according to a T2T strategy aiming at remission (defined as a Disease Activity Score in 28 joints (DAS28) < 2.6 (22)) including a treatment advice regarding subsequent DAS28-driven therapeutic steps (23). The aim of the present study was to evaluate the adherence to these T2T recommendations. We examined whether these recommendations resulted in regular assessment of the disease activity with the DAS28 and whether medication was adapted according to the treatment advice. Moreover, we explored reasons for non-adherence to the T2T recommendations.

Patients and methods

Patients

Recommendations regarding T2T were implemented in six hospitals in The Netherlands in January 2006, as part of the DREAM remission induction cohort. Inclusion of patients into the cohort and data collection are still ongoing. The cohort consists of consecutive patients newly diagnosed with RA who met the following inclusion criteria: clinical diagnosis of RA, age ≥ 18, symptom duration (defined as time from first reported symptom to diagnosis of RA by rheumatologist) of one year or less, a DAS28 ≥ 2.6, and no previous treatment with disease-modifying antirheumatic drugs (DMARDs) and/or prednisolone. Under Dutch law, this descriptive evaluation does not need approval from an ethical review board. Nonetheless, patients were fully informed, and informed consent was obtained.

For the present study, a random sample of 100 patients of the DREAM remission induction cohort was taken using the 'random sample of cases' function in SPSS. We selected patients who had a minimal follow-up of six months to ensure that every patient had at least three follow-up evaluations.

Treatment

After inclusion, visits were scheduled at weeks 8, 12, 20, 24, 36, and 52, and every three months thereafter. Patients could visit the rheumatologist in between the scheduled cohort visits when necessary. The T2T recommendations included systematic monitoring of the disease activity with the DAS28 in combination with a treatment advice regarding predefined treatment adjustments aiming at remission (defined as a DAS28 < 2.6). Therapy consisted of initial methotrexate monotherapy (MTX), followed by the addition of sulfasalazine (SSZ) in case of non-remission, and thereafter, sulfasalazine was exchanged for anti-tumor necrosis factor (TNF) α agents in case of moderate or high disease activity (Table 1). If the target of DAS28 < 2.6 was reached, medication was not changed. In case of sustained remission (≥ six months), medication was gradually tapered and eventually discontinued. The last introduced medication was tapered first (i.e. MTX was always tapered as last). The tapering steps were as follows (all lasting six months): MTX in mg/week, 25-15-7.5-stop; SSZ in mg/day, 3000-2000-1000-stop; adalimumab 40 mg, every week-every two weeks-stop; etanercept 50 mg, every week-every two weeks-stop; infliximab 3 mg/kg, every four weeks-every eight weeks-stop. In case of a disease flare-up (DAS28 ≥ 2.6), the most recently effective medication (dosage) was reintroduced and treatment could be subsequently intensified.

Deviations from the protocol were allowed on clinical indication. In patients with sulfa allergy, SSZ was replaced by hydroxychloroquine at 400 mg per day. Nonsteroidal anti-inflammatory drugs, prednisolone ≤ 10 mg per day and intra-articular corticosteroid injections were allowed at clinical indication. Details of the protocol were reported earlier (23). All clinical data on patient characteristics, clinical and laboratory measures, and medication use were prospectively stored in an electronic database.

Table 1. Treatment protocol.

Follow-up	DAS28	Medication
Week 0	≥2.6	MTX 15 mg/week
Week 8	≥2.6	MTX 25 mg/week
Week 12	≥2.6	MTX 25 mg/week + SSZ 2,000 mg/day
Week 20	≥2.6	MTX 25 mg/week + SSZ 3,000 mg/day
Week 24	≥3.2†	MTX 25 mg/week + ADA 40 mg every 2 weeks
Week 36	≥2.6 and decrease of >1.2‡	MTX 25 mg/week + ADA 40 mg/week
Week 52	≥3.2†	MTX 25 mg/week + etan. 50 mg/week
1 year + 3 months	≥3.2†	MTX 25 mg/week + inflix. 3 mg/kg every 8 weeks (after a loading dose at weeks 0, 2, and 6)
1 year + 6 months	≥2.6 and decrease of >1.2‡	MTX 25 mg/week + inflix. 3 mg/kg every 4 weeks

The goal of treatment was remission (Disease Activity Score in 28 joints (DAS28) < 2.6). Treatment was intensified when this target was not met. In case of remission, medication was not changed.

† Following the guidelines of the Dutch Society of Rheumatology and Dutch reimbursement regulations, anti-tumor necrosis factor α (anti-TNFα) therapy could be prescribed to patients with at least moderate disease activity (DAS28 ≥ 3.2) and in whom treatment with at least 2 disease-modifying antirheumatic drugs had failed (including methotrexate at 25 mg/week).

‡ Anti-TNFα therapy could be continued only if the DAS28 had decreased by > 1.2 after three months.

Measures

The following variables were collected at baseline: age, sex, symptom duration, fulfilment of the American College of Rheumatology (ACR) 1987 criteria for the classification of RA (24), rheumatoid factor (RF) status, anti-cyclic citrullinated peptide antibody status, C-reactive protein (CRP), patient's global assessment of pain on a 100-mm visual analogue scale (VAS), the disability index of the Dutch version of the Health Assessment Questionnaire (25,26), and component summary scores for physical and mental health of the 36-item Short Form Health Survey (27).

At every visit, joint counts were performed by trained rheumatology nurses, erythrocyte sedimentation rate (ESR) was measured and general health was filled out on a 100-mm VAS by the patient. The nurse calculated the DAS28 score and provided this, including the values of its components, to the rheumatologist.

Remission was defined as a DAS28 < 2.6. Remission according to the provisional ACR/EULAR Boolean-based definition of remission in RA was also examined, which required a tender joint count in 28 joints (TJC28) ≤ 1, swollen joint count in 28 joints (SJC28) ≤ 1, CRP ≤ 1 mg/dl and patient global assessment (PGA, on a 0-10 scale) ≤ 1 (28).

Data extraction

All scheduled clinical visits were retrieved from the database and parameters for disease activity and medication were extracted. A medical chart review was performed to determine whether the clinical decisions were compliant to the above described recommendations.

Deviations from the treatment advice were classified as: not intensifying (i.e. continuing/tapering/discontinuing) instead of intensifying treatment; intensifying instead of not intensifying (i.e. continuing/tapering/discontinuing) treatment; continuing instead of tapering/discontinuing treatment; tapering/discontinuing instead of continuing treatment; and other deviations. We registered whether the deviations concerned conventional DMARDs or anti-TNF therapy. Possible reasons for non-adherence were retrieved from the medical chart. Medication use outside the treatment advice (including the use of prednisolone dosages > 10 mg per day) was registered.

Statistical analysis

The primary outcome measures were the number of cohort visits in which the DAS28 was assessed and the number of these visits in which therapy was adapted according to the treatment advice, stratified by remission state (yes/no). The various deviations were reported as numbers with corresponding percentages. Pie charts were used to graphically present the extent to which the medication protocol was followed.

To test differences in the patient baseline characteristics between hospitals, we used independent *t* tests for normally distributed variables, chi-square tests for categorical variables, and Mann-Whitney U tests for non-normally distributed variables.

The level of significance was set at a p value < 0.05. Statistical analyses were performed using the statistical software package SPSS 18.0 (SPSS Inc., Chicago, IL, USA).

Results

Study sample

The baseline characteristics of the 100 patients whose medical charts were examined are presented in Table 2. This study group reflects a normal early RA population with 61.0% of the patients being female, a mean (standard deviation, SD) age of 57.7 (15.4), 61.0% RF positivity, and a mean DAS28 (SD) of 4.9 (1.1). Patients' baseline characteristics were comparable between hospitals (data not shown), except for symptom duration which differed between two hospitals; median (interquartile range, IQR) of 10.0 (6.5-16.0) versus 21.0 (9.8-30.3) weeks, *p*=0.012. The baseline characteristics of the patients who were not included in this study, did not differ significantly or clinically relevantly from the random sample of patients who were included in this study (not shown).

The 100 patients contributed to a total of 1115 visits. The mean (SD) follow-up time at the time of data collection in these patients was 28.0 (10.0) months. The mean (SD) number of cohort visits per patient was 10.9 (3.6).

Table 2. Description of the characteristics of the 100 rheumatoid arthritis (RA) patients.

Age, mean ± SD years	57.7 ± 15.4
Female sex, n (%)	61 (61.0)
Symptom duration, median (IQR) weeks	12.0 (8.0-25.0)
Fulfillment of ACR 1987 criteria for RA, n (%)	81/97 (83.5)
RF positive, n (%)	61 (61.0)
Anti-CCP positive, n (%)	58/98 (59.2)
DAS28, mean ± SD	4.9 ± 1.1
No. of swollen joints (28 assessed), median (IQR)	7.0 (4.0-12.0)
No. of tender joints (28 assessed), median (IQR)	4.0 (2.0-10.0)
ESR, median (IQR) mm/hour	31.2 ± 18.5
CRP, median (IQR) mg/litre	11.5 (5.0-30.8)
Patient's assessment of general health, mean ± SD (0-100 VAS)	54.0 ± 22.5
Patient's assessment of pain, mean ± SD (0-100 VAS)	51.7 ± 23.0
HAQ score, mean ± SD	0.9 ± 0.7
SF-36 PCS score, mean ± SD	38.3 ± 10.0
SF-36 MCS score, mean ± SD	47.8 ± 12.6

ACR, American College of Rheumatology; anti-CCP, anti–cyclic citrullinated peptide; CRP, C-reactive protein; DAS28, Disease Activity Score in 28 joints; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; IQR, interquartile range; MCS, mental component summary; PCS, physical component summary; RF, rheumatoid factor; SD, standard deviation; SF-36, Short-Form 36 health survey; VAS, visual analog scale.

Monitoring of disease activity

The DAS28 was available in 97.9% (1092/1115) of the scheduled cohort visits. The main reasons for the DAS28 score being missing were that the ESR was not (yet) available or the patient's general health was not assessed (data not shown). Since the level of disease activity could not be evaluated in these visits, we could not determine whether adherence to the medication protocol was accomplished. Therefore, these 23 visits (2.1%) were excluded from further analyses.

According to the T2T strategy, disease activity should be assessed using the DAS28 at least every three months. In 88.3% (964/1092) of the visits, this recommendation was met. In the remaining 128 cases, DAS28 remission was present at the previous visit in 71.1% (91/128), and, therefore, the attending rheumatologist scheduled the next visit in six months in 93.4% (85/91) of these visits.

Adherence treatment advice

Adherence to the treatment advice was observed in 69.3% (757/1092) of the visits. Non-adherence at least at one visit was experienced by 91.0% of patients (91/100).

Remission

Remission was present in 50.6% (553/1092) of the visits. The treatment advice was followed in 80.5% (445/553) of these visits, i.e. medication was continued or, in case of sustained remission (DAS28 < 2.6 for at least six months), tapered or discontinued (Figure 1A). The various deviations in the non-adherence cases (19.5%, 108/553) are also depicted in Figure 1A. Most frequently, medication was tapered or discontinued when it should have been continued according to the treatment advice (7.2%, 40/553), or treatment was continued when it should have been tapered of discontinued (6.2%, 34/553). Furthermore, medication was intensified in 4.3% (24/553) in spite of DAS28 remission. In 9 of these 24 cases, the patient had at least one swollen joint. Other deviations were observed in 1.8% (10/553). In 12.0% (13/108) of these non-adherence cases, the deviation concerned anti-TNF therapy.

The reasons for non-adherence are presented in Table 3. The most frequently observed reasons for non-adherence were the presence of active disease according to the rheumatologist (i.e. based on the presentation of the patient's overall disease activity, in particular the degree of arthritis) and drug side effects.

Remission according to the provisional ACR/EULAR definition of remission was observed in 42.9% (237/524) of these visits (remission could not be evaluated in all visits due to missing values for CRP).

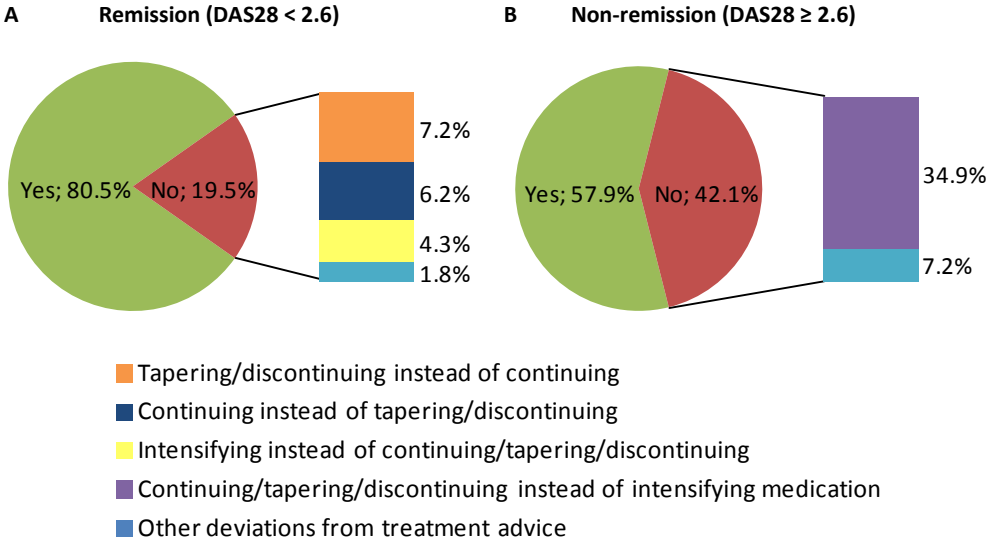

Figure 1. Adherence to the treatment advice of the treat-to-target strategy. The pie charts illustrate how often the treatment advice was followed in A) 553 visits in which remission (Disease Activity Score in 28 joints (DAS28) < 2.6) was present and B) 539 visits in which no remission (DAS28 ≥ 2.6) was present of 100 patients with early rheumatoid arthritis.

Non-remission

In case of non-remission, the treatment advice was followed in 57.9% (312/539) of the visits (Figure 1B), meaning that therapy was intensified. Figure 1B also shows the various deviations in case of non-adherence (42.1%, 227/539). The most frequently observed deviation was that medication was not intensified (i.e. continued, tapered or discontinued) when an intensification step should have been taken according to the treatment advice (34.9%, 188/539). Other deviations were observed in 7.2% (39/539). In 21.6% (49/227) of the non-adherence cases, the deviation concerned anti-TNF therapy.

In the non-adherence cases, disease activity was low (2.6 ≤ DAS28 ≤ 3.2) in 43.2% (98/227), moderate (3.2 < DAS28 ≤ 5.1) in 49.8% (113/227), and high (DAS28 > 5.1) in 7.0% (16/227).

Table 3 presents the reasons for non-adherence. The most frequently observed reason for deviation was that clinical remission was present according to the rheumatologist, even though the DAS28 was 2.6 or higher. In these 108 visits, the distribution of the clinical variables was as follows: median (IQR) SJC28 of 1.0 (0.0-3.0), median (IQR) TJC28 of 0.0 (0.0-3.0), mean (SD) ESR of 22.6 (14.9), and median (IQR) CRP of 5.0 (4.0-8.0). The mean (SD) DAS28 was 3.3 (0.7) and 54.6% (59/108) of these patients had

a DAS28 ≤ 3.2 The mean (SD) score of the patient's assessment of pain was 31.6 (21.4) and of general health 34.6 (21.1).

Non-remission according to the provisional ACR/EULAR definition of remission was observed in 94.2% (508/514) of these visits (remission could not be evaluated in all visits due to missing values for CRP).

Table 3. Reasons for non-adherence to the treatment advice of the treat-to-target strategy. Data are presented of a total of 1097 visits of 100 patients with early rheumatoid arthritis, stratified by remission state according to the Disease Activity Score in 28 joints (DAS28).

	Remission (DAS28 < 2.6) (n=553)	**Non-remission (DAS28 ≥ 2.6) (n=539)**
Tapering/discontinuing instead of continuing	40 (7.2)	.
Unknown	12	
Patient wish	3	
Side effects	19	
Clinical remission	5	
Other	1	
Continuing instead of tapering/discontinuing	34 (6.2)	.
Unknown	23	
Patient wish	4	
Active disease	5	
Other	2	
Intensifying instead not intensifying*	24 (4.3)	.
Unknown	2	
Patient wish	2	
Active disease	20	
Not intensifying* instead of intensifying	.	188 (34.9)
Unknown		29
Patient wish		13
Side effects		32
Clinical remission		106
Other		8
Other deviations from treatment advice	10 (1.8)	39 (7.2)
Unknown	5	10
Patient wish	.	2
Side effects	4	16
Clinical remission	.	2
Other	1	9

Values regarding the type of deviation are presented as number (%), values regarding the reasons for non-adherence are presented as number.

*Including continuing, tapering and discontinuing medication.

Other medication

Disease modifying medication outside the treatment advice was prescribed in 8.0% (8/100) of the patients; 1 patient received leflunomide and 7 patients received at least one intra-muscular corticosteroid injection. Prednisolone dosages > 10 mg per day were given to 7.0% (7/100) of the patients at least at one visit.

Drug side effects

Adherence to the treatment advice was prevented by drug side effects in 71 visits. Table 4 presents the various side effects that were registered in the medical charts. If the patient experienced more than one side effect, we listed only the first reported side effect.

Table 4. Drug side effects (n=71).

Not defined	23 (32.4)
Abnormal liver function tests	12 (16.9)
Nausea, abdominal pain or diarrhoea	10 (14.1)
Haematological abnormalities	7 (9.9)
Pulmonary problem	7 (9.9)
Mental or mood changes	5 (7.0)
Hair loss	3 (4.2)
Skin rash	2 (2.8)
Vision problem	2 (2.8)

Values are presented as number (%).

Discussion

This descriptive evaluation demonstrated that a T2T strategy is possible in daily clinical practice. The recommendations regarding T2T were successfully implemented in the participating rheumatology clinics of the DREAM remission induction cohort. Disease activity was regularly and systematically measured using the DAS28 and adherence to the treatment advice was high. In case of non-adherence to the recommendations, valid arguments for deviating were observed in the majority of these cases.

Real-life observational data regarding the adherence to a T2T strategy in daily clinical practice were analyzed. These are valuable data because T2T strategies are often conducted in the setting of randomized controlled trials (RCTs), which entails a more controlled environment compared to routine care. This was a retrospective evaluation, and, therefore, the attending physicians were not influenced by the goal of this analysis.

The successful implementation of T2T in the DREAM hospitals can be explained by several factors. First, the evidence from RCTs and, subsequently, the fact that current

guidelines and recommendations underline the importance of T2T has raised rheumatologists' awareness about the effectiveness of T2T. Second, the recommendations regarding the frequency of monitoring and the therapeutic regimen in the present study were fit in as close as possible with the conventional management of RA in daily clinical practice. Prior to the implementation of T2T, consensus was reached on the recommendations by all rheumatologists of the participating hospitals. Third, the organization of care was arranged as such that the treatment approach did not require extra effort and time from the rheumatologist during the clinical visit. Prior to the visit to the rheumatologist, RA disease activity according to the DAS28 was evaluated by a trained rheumatology nurse. The rheumatology nurses take part in annual DAS28 training sessions, which guarantee the uniformity of the DAS28 assessment. A previous study by Van Hulst *et al* suggests that nurse-led care including DAS28 measurement may be helpful in making DAS28 assessments more feasible for daily clinical practice settings (13). Furthermore, general practitioners are aware of the importance of early referral of patients with symptoms of arthritis to the rheumatologist, thereby making an early diagnosis possible.

At a percentage of 69%, the observed level of adherence to the T2T recommendations was probably optimal, as striving for 100% adherence is not realistic because treatment of patients is subject to side effects and comorbidities. Moreover, it is obvious that patients are involved in their treatment decision making process. Previous studies have shown that discordance exists between the patients' and rheumatologists' rating of disease activity (29,30) and that they approach the decision to intensify medication differently (31,32). Moreover, patients may be reluctant to change medications frequently and fear side effects. In the present study, the main reason for non-adherence was discordance between disease activity status according to the rheumatologist and the DAS28, which might be explained by properties of the DAS28 algorithm. The feet are omitted in the DAS28, however, disease activity in the feet joints is frequently observed in RA, even in patients who are considered to be in DAS28 remission (33). This among other factors has led to the debate whether the cut-off point for DAS28 remission reflects true clinical remission (34,35). In the therapeutic decision making, rheumatologists do not always rely solely on the DAS28 (36), but also other markers of inflammation and/or progression (31,37) and patients' characteristics (38) are taken into account. The DAS28 is suggested to be a tool to guide decision making in RA, nevertheless, it cannot always replace the clinical judgement in the context of an individual patient. Therefore, T2T should be performed with thoughtful consideration.

This study has some drawbacks. First, adherence to the recommendations of the T2T strategy was evaluated in only 100 patients of the total cohort, which includes more

than 700 patients at the time of data collection. However, a random sample was taken which we believe was representative for the total cohort. Second, it was not explicitly requested to report the reason for protocol deviations, and, therefore, not all reasons could be retrieved. Third, this T2T strategy reflects the effects of only one medication strategy; no other treatment strategies were included. Several therapeutic regimes and treatment approaches have been introduced over the last decade, but the most optimal strategy for patients newly diagnosed with RA remains undecided. Moreover, after the initiation of the DREAM remission induction cohort, it emerged that dose increase of anti-TNF therapy might have limited effectiveness (39) and also the effectiveness of a third anti-TNF agent in case of failure of two previous anti-TNF agents has been debated. This might have led to deviations from the advised anti-TNF therapy steps. Fourth, it was not investigated whether failure to be adherent to the strategy had any impact on whether patients achieved remission.

In conclusion, this study showed that the implementation of T2T is feasible in very early RA in daily clinical practice. We demonstrated a high adherence to the T2T recommendations, which comprised regular assessment of the DAS28 and a treatment advice regarding subsequent DAS28-driven therapeutic steps.

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References

1. Klarenbeek NB, Allaart CF, Kerstens PJ, Huizinga TW, Dijkmans BA**.** The BeSt story: on strategy trials in rheumatoid arthritis. Curr Opin Rheumatol. 2009;21:291-8.
2. McInnes IB, O'Dell JR**.** State-of-the-art: rheumatoid arthritis. Ann Rheum Dis. 2010;69:1898-906.
3. Smolen JS, Landewe R, Breedveld FC, Dougados M, Emery P, Gaujoux-Viala C, 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. Grigor C, Capell H, Stirling A, McMahon AD, Lock P, Vallance R, 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. Verstappen SM, Jacobs JW, van der Veen MJ, Heurkens AH, Schenk Y, ter Borg EJ, 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.
6. Fransen J, Moens HB, Speyer I, van Riel PL**.** 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.
7. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Kerstens PJ, Nielen MM, Vos K, van Schaardenburg D, et al. DAS-driven therapy versus routine care in patients with recent-onset active rheumatoid arthritis. Ann Rheum Dis. 2010;69:65-9.
8. Schipper LG, Vermeer M, Kuper HH, Hoekstra MO, Haagsma CJ, Broeder AA, et al. A tight control treatment strategy aiming for remission in early rheumatoid arthritis is more effective than usual care treatment in daily clinical practice: a study of two cohorts in the Dutch Rheumatoid Arthritis Monitoring registry. Ann Rheum Dis. 2012;71:845-50.
9. Schipper LG, van Hulst LT, Grol R, van Riel PL, Hulscher ME, Fransen J**.** 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.
10. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis: 2002 Update. Arthritis Rheum. 2002;46:328-46.
11. Smolen JS, Aletaha D, Bijlsma JW, Breedveld FC, Boumpas D, Burmester G, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis. 2010;69:631-7.

12. Haraoui B, Smolen JS, Aletaha D, Breedveld FC, Burmester G, Codreanu C, et al. Treating Rheumatoid Arthritis to Target: multinational recommendations assessment questionnaire. Ann Rheum Dis. 2011;70:1999-2002.
13. van Hulst LT, Creemers MC, Fransen J, Li LC, Grol R, Hulscher ME, et al. How to improve DAS28 use in daily clinical practice?--a pilot study of a nurse-led intervention. Rheumatology (Oxford) 2010;49:741-8.
14. Littlejohn G, Tymms KE**.** Multi-Centre, Observational Study Shows High Proportion of Australian Rheumatoid Arthritis Patients Have Inadequate Disease Control. Arthritis Rheum. 2010;62(Suppl 10):320.
15. Tymms K, Littlejohn G**.** The MDA study - a multi-centre, cross-sectional, study of barriers to optimal control for rheumatoid arthritis patients with moderate and high disease activity. Ann Rheum Dis. 2011;70(Suppl3):76.
16. Lacaille D, Anis AH, Guh DP, Esdaile JM**.** Gaps in care for rheumatoid arthritis: a population study. Arthritis Rheum. 2005;53:241-8.
17. Kievit W, Fransen J, Oerlemans AJ, Kuper HH, van der Laar MA, de Rooij DJ, et al. The efficacy of anti-TNF in rheumatoid arthritis, a comparison between randomised controlled trials and clinical practice. Ann Rheum Dis. 2007;66:1473-8.
18. Verschueren P, Westhovens R**.** Optimal care for early RA patients: the challenge of translating scientific data into clinical practice. Rheumatology (Oxford). 2011;50:1194-200.
19. Harrold LR, Harrington JT, Curtis JR, Furst DE, Bentley MJ, Shan Y, et al. Prescribing practices in a US cohort of rheumatoid arthritis patients before and after publication of the American College of Rheumatology treatment recommendations. Arthritis Rheum. 2012;64:630-8.
20. Sokka T, Pincus T**.** Most patients receiving routine care for rheumatoid arthritis in 2001 did not meet inclusion criteria for most recent clinical trials or american college of rheumatology criteria for remission. J Rheumatol. 2003;30:1138-46.
21. Hoekstra M, van de Laar MA, Bernelot Moens HJ, Kruijsen MW, Haagsma CJ**.** Longterm observational study of methotrexate use in a Dutch cohort of 1022 patients with rheumatoid arthritis. J Rheumatol. 2003;30:2325-9.
22. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL**.** 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.
23. Vermeer M, Kuper HH, Hoekstra M, Haagsma CJ, Posthumus MD, Brus HL, et al. Implementation of a treat-to-target strategy in very early rheumatoid arthritis:

results of the Dutch Rheumatoid Arthritis Monitoring remission induction cohort study. Arthritis Rheum. 2011;63:2865-72.
24. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988;31:315-24.
25. Fries JF, Spitz P, Kraines RG, Holman HR**.** Measurement of patient outcome in arthritis. Arthritis Rheum. 1980;23:137-45.
26. Siegert CE, Vleming LJ, Vandenbroucke JP, Cats A**.** Measurement of disability in Dutch rheumatoid arthritis patients. Clin Rheumatol. 1984;3:305-9.
27. Ware JE, Jr., Sherbourne CD**.** The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30:473-83.
28. Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LH, Funovits J, et al. American college of rheumatology/european league against rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Ann Rheum Dis. 2011;70:404-13.
29. Barton JL, Imboden J, Graf J, Glidden D, Yelin EH, Schillinger D**.** Patient-physician discordance in assessments of global disease severity in rheumatoid arthritis. Arthritis Care Res (Hoboken). 2010;62:857-64.
30. Khan NA, Spencer HJ, Abda E, Aggarwal A, Alten R, Ancuta C, et al. Determinants of discordance in patients' and physicians' rating of rheumatoid arthritis disease activity. Arthritis Care Res (Hoboken). 2012;64:206-14.
31. van Hulst LT, Kievit W, van Bommel R, van Riel PL, Fraenkel L**.** Rheumatoid arthritis patients and rheumatologists approach the decision to escalate care differently: results of a maximum difference scaling experiment. Arthritis Care Res (Hoboken). 2011;63:1407-14.
32. Wolfe F, Michaud K**.** Resistance of rheumatoid arthritis patients to changing therapy: discordance between disease activity and patients' treatment choices. Arthritis Rheum. 2007;56:2135-42.
33. van der Leeden M, Steultjens MP, van Schaardenburg D, Dekker J**.** Forefoot disease activity in rheumatoid arthritis patients in remission: results of a cohort study. Arthritis Res Ther. 2010;12:R3.
34. Makinen H, Kautiainen H, Hannonen P, Sokka T**.** Is DAS28 an appropriate tool to assess remission in rheumatoid arthritis? Ann Rheum Dis. 2005;64:1410-3.
35. Landewe R, van der Heijde D, van der Linden S, Boers M**.** 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.

36. Taylor WJ, Harrison AA, Highton J, Chapman P, Stamp L, Dockerty 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.
37. Lindsay K, Ibrahim G, Sokoll K, Tripathi M, Melsom RD, Helliwell PS**.** The composite DAS Score is impractical to use in daily practice: evidence that physicians use the objective component of the DAS in decision making. J Clin Rheumatol. 2009;15:223-5.
38. Kievit W, van Hulst L, van Riel P, Fraenkel L**.** Factors that influence rheumatologists' decisions to escalate care in rheumatoid arthritis: results from a choice-based conjoint analysis. Arthritis Care Res (Hoboken). 2010;62:842-7.
39. Blom M, Kievit W, Kuper HH, Jansen TL, Visser H, den Broeder AA, et al. Frequency and effectiveness of dose increase of adalimumab, etanercept, and infliximab in daily clinical practice. Arthritis Care Res (Hoboken). 2010;62:1335-41.

Chapter 6 |

Treat-to-target in early rheumatoid arthritis: an initial investment but probably cost-saving in the end. A study of two cohorts in the DREAM registry

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Abstract

Objectives. To analyse the cost-effectiveness and cost-utility of a treat-to-target (T2T) strategy compared to usual care (UC) in rheumatoid arthritis (RA) over the first three years of the disease.

Methods. Two differently treated cohorts of early RA patients who fulfilled the American College of Rheumatology criteria for RA were compared. The T2T cohort was treated according to a protocolised strategy aiming at remission (Disease Activity Score in 28 joints (DAS28) < 2.6). The UC cohort was treated without DAS28-guided treatment decisions. EuroQol-5D utility scores were estimated from the Health Assessment Questionnaire. A health care perspective was adopted and direct medical costs were collected. The incremental cost effectiveness ratio (ICER) per patient in remission and incremental cost utility ratio (ICER) per quality adjusted life year (QALY) gained were calculated over two and three years of follow-up.

Results. Two year data were available for 261 T2T patients and 213 UC patients; an extended follow-up of three years was available for 127 and 180 patients, respectively. T2T produced higher remission percentages and a larger gain in QALYs than UC. The ICER was € 3,591 per patient in remission after two years and T2T was dominant after three years. The ICER was € 19,410 per QALY after two years and T2T was dominant after three years.

Conclusions. Over the first two years of treatment, T2T is associated with higher costs but also with substantial higher effectiveness compared with UC. In the third year, T2T probably becomes cost-saving.

Introduction

Treat-to-target (T2T) has become the new paradigm for the treatment of patients with rheumatoid arthritis (RA) (1). The key elements of T2T are: monitoring disease activity, subsequently adjusting medication in accordance to a fixed protocol, and aiming at a predefined target. Clinical trials have demonstrated that a T2T approach is more effective in lowering disease activity and, ultimately, reaching remission than usual care (2-7).

The Dutch Rheumatoid Arthritis Monitoring (DREAM) remission induction cohort has demonstrated that a T2T strategy aiming for remission (Disease Activity Score in 28 joints (DAS28) < 2.6 (8)) is very effective in daily clinical practice, with percentages of DAS28 remission ranging from 47% after six months to 58% after twelve months (9). In this early RA cohort, remission was achieved rapidly with a median time to first remission of 25 weeks. Moreover, this T2T strategy resulted in beneficial clinical outcomes after one year compared to usual care treatment (7).

Early and effective suppression of disease activity is expected to reduce pain, prevent progression of joint damage and disability (10,11), and increase the patient's quality of life (12,13). The concept of T2T assumes that intensive efforts and costs are made in the beginning of the disease to gain health and cost savings later. However, the question is whether indeed the health benefits outweigh the extra costs associated with performing a T2T approach.

The objective of this study is to evaluate the cost-effectiveness and cost-utility, from a health care perspective, of a T2T strategy aiming at remission compared to usual care for the treatment of early RA patients in daily clinical practice over a period of up to three years.

Patients and methods

Study design

This was a quasi-experimental study in which two differently treated cohorts of early RA patients were compared. Both cohorts originate from rheumatology centres in two different regions in the eastern part of The Netherlands. In The Netherlands, all RA patients are treated by centre-based rheumatologists. The T2T cohort consisted of patients from the DREAM remission induction cohort and the usual care (UC) cohort consisted of patients from the Nijmegen early RA inception cohort (14). This study can be defined as a quasi-experiment because unselected patients were included in both cohorts with 'living area' as main determinant for being included in either one of the cohorts. In both cohorts, all clinical data on patient characteristics, medication, clinical and laboratory

measures were assessed in a standardized way and stored prospectively in electronic databases. Currently, in both cohorts, new patients are still being included and follow-up continues. The hospitals' ethics committees determined, in accordance with Dutch law, that no approval was required since the studies contain data from daily clinical practice. Nonetheless, patients were fully informed and informed consent was obtained.

Treat-to-target

Since January 2006, patients were enrolled in the DREAM remission induction cohort (9). A T2T strategy including standardised and protocolised treatment adjustments aiming at remission (DAS28 < 2.6) was applied. Patients visited the clinic at weeks 0, 8, 12, 20, 24, 36 and 52, and every three months thereafter. Therapy consisted of initial methotrexate monotherapy (MTX), followed by the addition of sulfasalazine (SSZ), and thereafter in the case of persistent disease activity, sulfasalazine was replaced with anti-tumour necrosis factor (TNF) α agents. If the target of DAS28 < 2.6 was met, medication was not changed. In case of sustained remission (≥ six months), medication was gradually reduced and eventually discontinued. Nonsteroidal anti-inflammatory drugs (NSAIDs), prednisolone at a dosage of ≤ 10 mg/day, and intra-articular corticosteroid injections were allowed at the discretion of the attending rheumatologist. Data collection, including assessment of the DAS28, was performed by trained rheumatology nurses.

Usual care

In the usual care cohort, patients were regularly assessed every three months, but treatment decisions could be made at any time at the discretion of the treating rheumatologist. At every follow-up, the DAS28 was assessed by trained rheumatology nurses. In contrast to a T2T approach, the DAS28 values were not generally provided to the treating rheumatologist and pharmacological treatment was not protocolised but at the discretion of the rheumatologist. In general, patients were treated with step-up or sequential monotherapy with conventional disease-modifying antirheumatic drugs (DMARDs) and/or biologic, notably anti-TNF. Prednisolone (oral or injections) and NSAIDs could also be used. The most commonly applied strategy was starting with MTX monotherapy, subsequently switching to SSZ or adding SSZ in case of MTX failure, and adding an anti-TNF agent after two or more DMARDs had failed.

Selection of patients

For the current study, we selected patients from both cohorts who fulfilled the following inclusion criterion: RA according to the American College of Rheumatology (ACR) 1987 classification criteria for RA (15), age ≥ 18 years, disease duration of less than one year,

and no previous treatment with DMARDs. Patients diagnosed between January 2000 and February 2009 with a minimal follow-up of two years were selected. The DREAM remission induction cohort started in 2006, but to increase statistical power we were forced to include patients for the UC group diagnosed from January 2000 onwards. Although clinical practice might have changed over calendar years, biologic agents were already available for use in daily practice and tight control principles have been introduced since then. Patients from the T2T cohort visited the Medisch Spectrum Twente, Enschede, Ziekenhuisgroep Twente, Almelo/Hengelo or Isala Klinieken, Zwolle. Patients from the UC cohort visited the Radboud University Nijmegen Medical Centre or Maartenskliniek, Nijmegen.

Measurements

The effectiveness of treatment was evaluated using the DAS28 (calculated using the erythrocyte sedimentation rate (ESR)). A DAS28 < 2.6 was defined as remission (16).

Utilities were estimated to evaluate the effect of treatment on health related quality of life. Utility is the valuation of a health state on a scale of 0 (equivalent to death) to 1 (equivalent to full health) and is used to derive quality-adjusted life years (QALYs) (17). Because preference based measures were not prospectively assessed, EuroQol-5D (EQ-5D) values (18) were estimated from the Health Assessment Questionnaire (HAQ) scores (19,20) by using model 5 of the mapping method by Bansback *et al* (21). This model was reported to be the most successful of the five mapping methods, by having the lowest mean square error and the best predictive value (21,22). Concordantly, the QALYs were computed according to the trapezium rule.

Cost analysis

The cost analysis exists of two main parts. First, on patient level, volumes of care related to the T2T strategy or usual care were determined. Volumes of hospital related care, i.e. consultations with the rheumatologist and the rheumatology nurse, telephonic consultations (rheumatologist), and hospital admissions related to RA, were retrieved from the hospital information system. Medication use (exact dose of medication and administration period) was prospectively registered in the electronic case report forms.

The second part of the cost analysis consisted of determining the cost prices for each volume of consumption. Volumes of care were multiplied by the cost prices for each volume of care to calculate costs. The standard cost prices from the Dutch Guideline for Cost Analyses were used for hospital related care (see Appendix) (23). The price based on personnel, material and overhead of day care hospital admissions required for treatment with infliximab or rituximab was estimated at a mean of € 122 per day (on top of the

medication costs). Cost prices for medication were retrieved from the Dutch national tariff list provided by the Dutch Board of Health Insurances (23). The base year was 2011 for all prices. Prices retrieved from other years were converted to 2011 euros using the general Dutch price index rate (24).

Statistical analysis

Data of two year follow-up were analysed as well as an extended follow-up of three years in patients who had sufficient follow-up. Our expectation was that on the long-term, costs associated with performing T2T will decrease. In our previous study, the necessary sample size to detect a difference in remission of 20% between both groups was estimated to be at least 2x125=250 patients (7). This sample size estimation was satisfied in the two and three years data analyses in the present study.

The incremental cost-effectiveness ratio (ICER) was calculated by dividing the difference in costs by the difference in effectiveness (based on the number of patients in remission) derived from the two groups. This ICER is expressed as costs per one more patient in remission. The incremental cost-utility ratio (ICER) was calculated by dividing the difference in costs by the difference in the QALYs produced by the two groups. This ICER is expressed as costs per QALY gained. Uncertainty in both ratios was determined non-parametrically using bootstrap techniques. Results of the 1,000 bootstrapped replications are presented in cost-effectiveness planes which graphically present the uncertainty around the ratio of the two and three years data.

Missing values were imputed with single imputation using a regression method including a random component for the ESR, patient's assessment of general health, and HAQ question 23 (take a tub bath) or linear interpolation using the trapezoid method for the DAS28 and EQ-5D scores, conditional on the data being missing at random.

The level of significance was set at a p value < 0.05. Statistical analyses were performed using the statistical software package SPSS 18.0 (SPSS Inc., Chicago, IL, USA). The bootstrap was performed in Excel.

Results

Baseline characteristics

Two year follow-up data were available for 261 patients of the T2T cohort and for 213 patients of the UC cohort. An extended three year follow-up was available for a smaller proportion of patients due to insufficient follow-up; i.e. in 127 of the 261 (48.7%) T2T patients and 180 of the 213 (84.5%) UC patients. Baseline characteristics were comparable between patients with and without sufficient follow-up.

Table 1 presents the demographic and clinical characteristics of both groups at baseline. The groups were comparable at baseline regarding age, gender, rheumatoid factor (RF) positivity, number of tender joints (28 assessed) and ESR. Statistically significant but small differences were found for the mean DAS28, number of swollen joints (28 assessed), C-reactive protein, patient's assessment of global health and pain, and HAQ score, which were higher in the T2T group.

MTX monotherapy was the initial treatment in the T2T group by protocol. In the UC group, patients started with SSZ monotherapy (45.5%, 97/213), MTX monotherapy (43.7%, 93/213) or occasionally another DMARD (6.6%, 14/213) or no medication (4.2%, 9/213).

Table 1. Baseline characteristics of the patients of the treat-to-target (T2T) and usual care (UC) groups.

	T2T (n=261)	**UC (n=213)**
Age, mean ± SD years	57.9 ± 13.8	56.6 ±13.4
Female sex, n (%)	161 (61.7)	132 (62.0)
RF positive, n (%)	178 (68.2)	147/211 (69.7)
DAS28, mean ± SD	5.0 ± 1.1†	4.8 ± 1.2
No. of swollen joints (28 assessed), median (IQR)	8 (5-12)†	9 (6-13)
No. of tender joints (28 assessed), median (IQR)	5 (2-9)	4 (2-9)
ESR, median (IQR) mm/hour	28.0 (15.5-42.0)	26.0 (12.0-39.0)
CRP, median (IQR) mg/litre	14.0 (5.0-34.5)†	6.7 (0.0-27.8)
VAS general health, mean ± SD (0-100)	52.9 ± 22.6†	45.7 ± 23.0
VAS pain, mean ± SD (0-100)	51.2 ± 21.9†	44.9 ± 23.2
HAQ score, median (IQR)	1.1 (0.6-1.5) (n=244)†	0.9 (0.5-1.4) (n=151)

CRP, C-reactive protein; DAS28, Disease Activity Score in 28 joints; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; IQR, interquartile range; RF, rheumatoid factor; SD, standard deviation; VAS, visual analog scale.

† $P < 0.05$ for differences between groups.

Health outcomes

Table 2 presents the health outcome results after two and three years of follow-up. After two years, 64.4% (168/261) of the T2T group was in remission versus 34.7% (74/213) of the UC group ($p < 0.001$). Over the first two years of treatment, the median (IQR) of QALYs was higher in the T2T group than in the UC group (1.45 (1.24-1.55) versus 1.39 (1.18-1.53), respectively, p=0.04).

After three years, the remission percentages were 59.8% (76/127) with T2T versus 35.0% (63/180) with UC ($p < 0.001$). The median (IQR) of QALYs over the first three

years was higher in the T2T group than in the UC group (2.19 (1.81-2.34) versus 2.04 (1.64-2.27), respectively, *p*=0.05).

Table 2. Health outcomes in the treat-to-target (T2T) and usual care (UC) groups after two and three years of follow-up.

	Two years		Three years	
	T2T (n=261)	**UC (n=213)**	**T2T (n=127)**	**UC (n=180)**
DAS28, mean ± SD	2.4 ± 1.0†	3.1 ± 1.3	2.5 ± 1.0†	3.1 ± 1.3
DAS28 level, n (%)				
Remission (DAS28 < 2.6)	168 (64.4)	74 (34.7)	76 (59.8)	63 (35.0)
Low (2.6 ≤ DAS28 ≤ 3.2)	48 (18.4)	44 (20.7)	28 (22.0)	35 (19.4)
Moderate (3.2 < DAS28 ≤ 5.1)	37 (14.2)	76 (35.7)	21 (16.5)	72 (40.0)
High (DAS28 > 5.1)	8 (3.1)	19 (8.9)	2 (1.6)	10 (5.6)
QALYs, median (IQR)	1.45	1.39	2.19	2.04
	(1.24-1.55)	(1.18-1.53)	(1.81-2.34)	(1.64-2.27)
	(n=221)†	(n=143)	(n=101)†	(n=106)

Quality adjusted life years (QALYs) were derived from the EuroQol-5D utility scores which were estimated from the Health Assessment Questionnaire (HAQ). QALYs could not be evaluated in all patients due to missing data in (items of) the HAQ.

DAS28, Disease Activity Score in 28 joints; SD, standard deviation.

† *P* < 0.05 for differences between groups.

Care consumption and costs

Table 3 presents the amount of care consumption and mean costs per patient during two and three years of follow-up. Over both periods, the numbers of consultations with the rheumatologist were comparable, whereas the numbers of consultations with the rheumatology nurse and telephonic consultations were higher in the T2T group. In usual care, more hospital admissions were observed than with T2T.

Over the first two years, the mean (SD) total costs per patient were € 4,791 (7,436) in the T2T group and € 3,727 (5,773) in the usual care group (Table 3). The observed difference in costs between groups was mainly generated by the costs of anti-TNF therapy and hospitalization. During the first two years of treatment, 21.5% (56/261) of the T2T group received anti-TNF therapy versus 15.0% (32/213) of the UC group.

Over the first three years, the mean (SD) total costs per patient were € 6,410 (10,845) in the T2T group and € 6,872 (11,033) in the UC group (Table 3). The observed difference in costs between groups was mainly generated by hospitalization.

Overall, the mean time until the first anti-TNF agent was started was shorter in the T2T group compared to the UC group (mean (SD) of 58 (29) weeks versus 80 (39) weeks, respectively, *p*=0.002).

Table 3. Mean volumes of care and total costs in euros per patient per period in the treat-to-target (T2T) and usual care (UC) groups after two and three years of follow-up.

	0-2 year				
	T2T (n=261)		UC (n=213)		
	Volume	Costs	Volume	Costs	Δ in costs
Consultations rheumatologist	10.4 ± 3.0	696 ± 199	10.3 ± 2.9	689 ± 195	7
Consultations nurse	8.8 ± 3.0†	588 ± 200†	7.8 ± 1.9	522 ± 127	66
Telephonic consultations	1.3 ± 1.8†	34 ± 46†	0.6 ± 1.4	16 ± 36	18
Hospital admissions	0.4 ± 2.7†	178 ± 1,208†	1.1 ± 4.2	521 ± 1,901	-343
Medication					
DMARDs/other		174 ± 165†		249 ± 340	-75
Anti-TNF		3,121 ± 7,162†		1,730 ± 4,905	1,391
Total		4,791 ± 7,436		3,727 ± 5,773	1,064‡
	0-3 year				
	T2T (n=127)		UC (n=180)		
	Volume	Costs	Volume	Costs	Δ in costs
Consultations rheumatologist	13.7 ± 3.3	917 ± 220	13.6 ± 3.3	909 ± 224	8
Consultations nurse	12.1 ± 3.6†	809 ± 244	8.9 ± 1.7	596 ± 117	213
Telephonic consultations	1.9 ± 2.1†	49 ± 54†	0.8 ± 1.7	21 ± 45	28
Hospital admissions	0.5 ± 3.2†	215 ± 1,441†	1.6 ± 5.0	748 ± 2,263	-533
Medication					
DMARDs/other		260 ± 335†		423 ± 612	-163
Anti-TNF		4,160 ± 10,685		4,175 ± 10,070	-15
Total		6,410 ± 10,845		6,872 ± 11,033	-462‡

Volumes are the mean ± standard deviation (SD).

Anti-TNF, anti-tumour necrosis factor; DMARDs, disease-modifying antirheumatic drugs.

† $P < 0.05$ for differences between groups.

‡ Bootstrapped 95% confidence intervals: 0-2 year, 1,026 to 1,121; 0-3 year, -513 to -350.

Cost-effectiveness

After two years of follow-up, the ICER was € 3,591 per patient in remission and after three years of follow-up the T2T strategy was dominant. Figure 1 presents the cost-effectiveness planes, showing the relation between the difference in effect (x-axis) and the difference in costs (y-axis) between T2T and UC. Figure 1A presents the two years data and shows that 91% of the bootstrapped ratios were situated in the upper-right quadrant, which signifies a gain in effectiveness against higher costs. Figure 1B shows that after three years, 64% of the bootstrapped ratios were situated in the lower-right quadrant, which signifies lower costs and higher effectiveness.

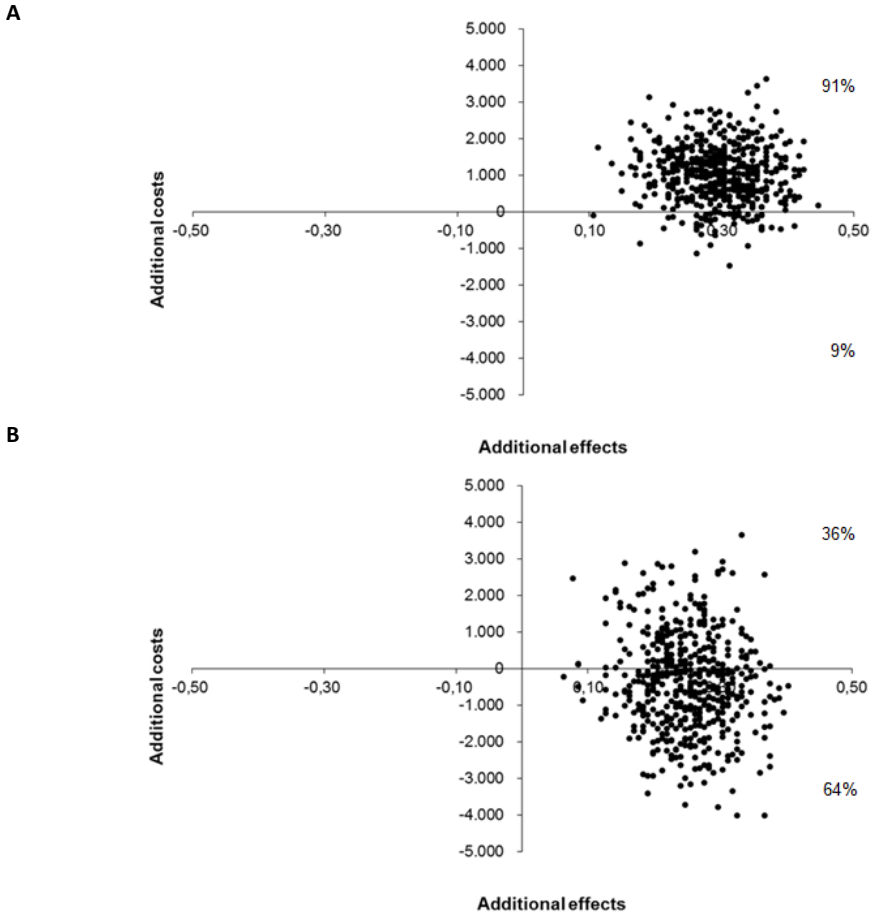

Figure 1. Cost-effectiveness planes of 1000 bootstrap replicates of the incremental cost and effectiveness (based on the number of patients in remission, defined as a Disease Activity Score in 28 joints < 2.6) of the treat-to-target strategy versus usual care in early rheumatoid arthritis after A) two years and B) three years of follow-up.

Cost-utility

Over a period of two years, the ICER was € 19,410 per QALY and after three years of treatment the T2T strategy was dominant. Figure 2 presents the cost-utility planes, showing the relation between the difference in QALYs (x-axis) and the difference in costs (y-axis) between T2T and UC. Figure 2A shows that after 94% of the two years' bootstrapped ratios were situated in the upper-right quadrant. Figure 2B shows that 66% of the three years' bootstrapped ratios were situated in the lower-right quadrant, which signifies lower costs and higher effectiveness.

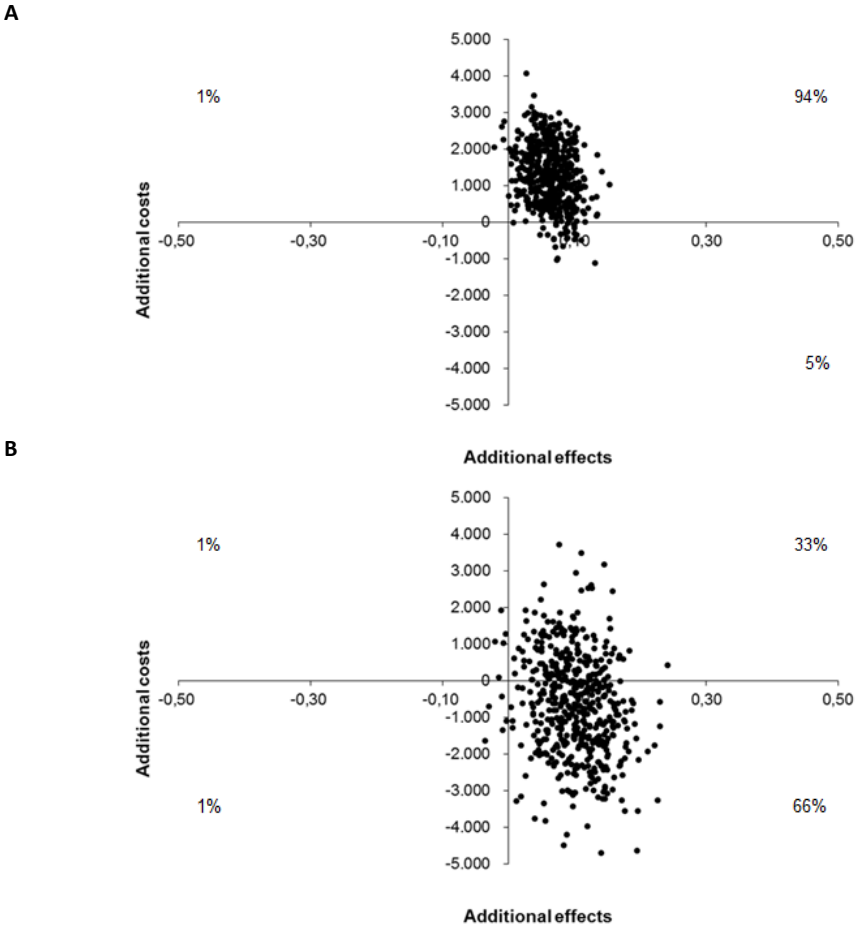

Figure 2. Cost-utility planes of 1000 bootstrap replicates of the incremental cost and quality-adjusted life years gained by the treat-to-target strategy versus usual care in early rheumatoid arthritis after A) two and B) three years of follow-up.

Discussion

According to the results of this cost-effectiveness and cost-utility analysis, T2T is the preferred strategy over UC. After two years of treatment, T2T is associated with higher costs, but also with substantially higher effectiveness. In the T2T group DAS28 remission had been achieved more frequently and there was a larger gain in health-related QALYs compared with UC. The ICER lies far below the threshold of €80,000 per QALY, which is considered to be an acceptable willingness to pay for one QALY in The Netherlands (25). Moreover, the costs to bring one more patient in remission also seem to be acceptable.

Results of an extended follow-up analysis of three year data were clearly in favor of T2T, with 66% chance of the T2T strategy being the dominant strategy as costs were lower whereas effectiveness was higher. To our knowledge, this is the first health economic evaluation of T2T in daily clinical practice.

The drivers of absolute costs and cost differences between T2T and UC were anti-TNF therapy and hospitalization. Our previous studies demonstrated that the majority of the T2T patients achieved remission with conventional DMARDs (7,9). According to the treatment protocol, anti-TNF was prescribed only for a minority of patients whose disease activity remained moderate to high after insufficient effect of conventional DMARDs, thereby preventing overtreatment with anti-TNF agents with their costs and side effects. In the UC group, anti-TNF was initiated later in the disease course, and, therefore, it might be less effective and longer required in patients. Costs due to hospitalization were directly related to RA. The higher number of hospital admissions in the UC group might be explained by less efficient disease control.

The principle of T2T is to aim at achieving and sustaining remission as early as possible. Our expectation is that the extra effort and time spent in the first years of the disease, ultimately result in a reduction of the number of consultations later in the disease course and the possibility of tapering and discontinuing medication in case of sustained remission, thereby diminishing costs. Therefore, we expect that on the long-term, cost savings associated with T2T will increase. Furthermore, better and earlier disease control might lead to more work participation on the long-term, which will ultimately lower the costs of T2T for society and improve quality of life for the patients.

An important strength of this study is the quasi-experimental design containing real-life observational data regarding effectiveness, health-related quality of life and costs of T2T compared with usual care. This is in contrast to many health economic evaluations, which often use modeling techniques with many underlying assumptions.

However, this study has some limitations also. First, patients were not randomised to one of the strategies compared. However, the fact that patients were unselected in both cohorts from different regions reduced confounding by indication to the minimum. Furthermore, no relevant differences in baseline characteristics which are prognostic for the treatment effect were found. Second, it should be noted that UC patients were included from 2000 until present, whereas T2T patients were included from 2006 until present. Even though the same treatment options for both groups were available during observation, one can assume that UC has changed between 2000 and 2006. Therefore, it would have been preferable to include only UC patients who were recruited from 2006 onwards. A sub-analysis omitting UC patients recruited prior to 2006 resulted in a lower number of UC patients, i.e. lower power, however, comparable

differences in outcomes and costs were observed, thereby coming to the same conclusions. Therefore, we believe that the comparison in the present study is appropriate. Furthermore, this study attempts to provide the best possible comparison currently available. A third limitation is that a preference based health-related quality of life measure was not available in the UC cohort, and, therefore, we estimated utilities from the HAQ. The HAQ has been shown to be highly correlated with health state utility values, which are used to calculate QALYs (26). Nevertheless, HAQ-derived utilities will only capture change in quality of life generated by the patient's functional status and not by other factors. We expect that T2T patients improve at more dimensions of quality of life than only function status. Therefore, we believe that this was a conservative analysis. We acknowledge that the use of a mapping method will always be suboptimal to primary collection of utility data. Fourth, we applied a health care perspective, thereby taking into account only direct medical costs. However, the economic burden of RA goes beyond health care costs (27-29) and a societal perspective would be preferable. RA leads to substantial losses in terms of work productivity which increases with disease duration (30,31). Unfortunately, data on work participation were not available. According to our view, we performed a conservative cost analysis and our expectations are that T2T, which decreases disease activity rapidly and early in the disease course, will have an additional positive effect on non-medical costs (e.g. work productivity, informal care, and paid housekeeping).

Having these limitations in mind, we feel that our results are an indication that T2T is in cost-effective. We conclude that the application of a T2T strategy aiming at remission in early RA is an expensive effort but probably cost-saving within three years compared with UC. Therefore, T2T can be recommended as the standard of care for the treatment of RA.

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References

1. Smolen JS, Aletaha D, Bijlsma JW, Breedveld FC, Boumpas D, Burmester G, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis. 2010;69:631-7.
2. Schoels M, Knevel R, Aletaha D, Bijlsma JW, Breedveld FC, Boumpas DT, et al. Evidence for treating rheumatoid arthritis to target: results of a systematic literature search. Ann Rheum Dis. 2010;69:638-43.
3. Knevel R, Schoels M, Huizinga TW, Aletaha D, Burmester GR, Combe B, 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.
4. Schipper LG, van Hulst LT, Grol R, van Riel PL, Hulscher ME, Fransen J**.** 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.
5. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Kerstens PJ, Nielen MM, Vos K, van Schaardenburg D, et al. DAS-driven therapy versus routine care in patients with recent-onset active rheumatoid arthritis. Ann Rheum Dis. 2010;69:65-9.
6. Soubrier M, Lukas C, Sibilia J, Fautrel B, Roux F, Gossec L, et al. Disease activity score-driven therapy versus routine care in patients with recent-onset active rheumatoid arthritis: data from the GUEPARD trial and ESPOIR cohort. Ann Rheum Dis. 2011;70:611-5.
7. Schipper LG, Vermeer M, Kuper HH, Hoekstra MO, Haagsma CJ, Broeder AA, et al. A tight control treatment strategy aiming for remission in early rheumatoid arthritis is more effective than usual care treatment in daily clinical practice: a study of two cohorts in the Dutch Rheumatoid Arthritis Monitoring registry. Ann Rheum Dis. 2012;71:845-50.
8. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL**.** 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.
9. Vermeer M, Kuper HH, Hoekstra M, Haagsma CJ, Posthumus MD, Brus HL, et al. Implementation of a treat-to-target strategy in very early rheumatoid arthritis: results of the Dutch Rheumatoid Arthritis Monitoring remission induction cohort study. Arthritis Rheum. 2011;63:2865-72.

10. van Tuyl LH, Boers M, Lems WF, Landewe RB, Han H, van der Linden S, et al. Survival, comorbidities and joint damage 11 years after the COBRA combination therapy trial in early rheumatoid arthritis. Ann Rheum Dis. 2010;69:807-12.
11. Krishnan E, Lingala B, Bruce B, Fries JF. Disability in rheumatoid arthritis in the era of biological treatments. Ann Rheum Dis. 2012;71:213-8.
12. Strand V, Khanna D. The impact of rheumatoid arthritis and treatment on patients' lives. Clin Exp Rheumatol. 2010;28(3 Suppl 59):S32-40.
13. Korthals-de Bos I, Van Tulder M, Boers M, Verhoeven AC, Ader HJ, Bibo J, et al. Indirect and total costs of early rheumatoid arthritis: a randomized comparison of combined step-down prednisolone, methotrexate, and sulfasalazine with sulfasalazine alone. J Rheumatol. 2004;31:1709-16.
14. Welsing PM, van Riel PL. The Nijmegen inception cohort of early rheumatoid arthritis. J Rheumatol Suppl. 2004;69:14-21.
15. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988;31:315-24.
16. Fransen J, Creemers MC, Van Riel PL. Remission in rheumatoid arthritis: agreement of the disease activity score (DAS28) with the ARA preliminary remission criteria. Rheumatology (Oxford). 2004;43:1252-5.
17. Cartwright WS. Methods for the economic evaluation of health care programmes, second edition. By Michael F. Drummond, Bernie O'Brien, Greg L. Stoddart, George W. Torrance. Oxford: Oxford University Press, 1997. J Ment Health Policy Econ. 1999;2:43.
18. Brooks R. EuroQol: the current state of play. Health Policy. 1996;37:53-72.
19. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum. 1980;23:137-45.
20. Siegert CE, Vleming LJ, Vandenbroucke JP, Cats A. Measurement of disability in Dutch rheumatoid arthritis patients. Clin Rheumatol. 1984;3:305-9.
21. Bansback N, Marra C, Tsuchiya A, Anis A, Guh D, Hammond T, et al. Using the health assessment questionnaire to estimate preference-based single indices in patients with rheumatoid arthritis. Arthritis Rheum. 2007;57:963-71.
22. Harrison MJ, Lunt M, Verstappen SM, Watson KD, Bansback NJ, Symmons DP. Exploring the validity of estimating EQ-5D and SF-6D utility values from the health assessment questionnaire in patients with inflammatory arthritis. Health Qual Life Outcomes. 2010;8:21.
23. Dutch Board of Health Insurances: Dutch Guideline for Cost Analyses. 2010.
24. Statistics Netherlands. www.cbs.nl (accessed 28 November 2011).

25. Raad voor Volksgezondheid en Zorg: Zinnige en Duurzame Zorg. 2006.
26. Marra CA, Woolcott JC, Kopec JA, Shojania K, Offer R, Brazier JE, et al. A comparison of generic, indirect utility measures (the HUI2, HUI3, SF-6D, and the EQ-5D) and disease-specific instruments (the RAQoL and the HAQ) in rheumatoid arthritis. Soc Sci Med. 2005;60:1571-82.
27. Kvien TK**.** Epidemiology and burden of illness of rheumatoid arthritis. Pharmacoeconomics. 2004;22(2 Suppl 1):1-12.
28. Zhang W, Anis AH**.** The economic burden of rheumatoid arthritis: beyond health care costs. Clin Rheumatol. 2011;30 Suppl 1:S25-32.
29. Boonen A, Severens JL**.** The burden of illness of rheumatoid arthritis. Clin Rheumatol. 2011;30 Suppl 1:S3-8.
30. Verstappen SM, Bijlsma JW, Verkleij H, Buskens E, Blaauw AA, ter Borg EJ, et al. Overview of work disability in rheumatoid arthritis patients as observed in cross-sectional and longitudinal surveys. Arthritis Rheum. 2004;51:488-97.
31. Neovius M, Simard JF, Askling J**.** How large are the productivity losses in contemporary patients with RA, and how soon in relation to diagnosis do they develop? Ann Rheum Dis. 2011;70:1010-5.

Appendix

Cost prices 2011

Consult at rheumatologist (13 minutes)	€ 66.90
Consult at rheumatology nurse (20 minutes)	€ 66.90
Telephonic consult at rheumatologist (5 minutes)	€ 25.73
Hospital day care related to biologics	€ 122.13
Hospital admission (one day)	€ 454.69

Chapter 7 |

The provisional ACR/EULAR definition of remission in RA: a comment on the patient global assessment criterion

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Abstract

Objectives. The provisional ACR/European League Against Rheumatism (EULAR) definition of remission in RA requires a score of ≤1 on the patient global assessment (PGA, 0-10 scale). We explored the relation between the PGA criterion and the patient's clinical disease state in an observational dataset.

Methods. Data of 512 newly diagnosed RA patients of the Dutch Rheumatoid Arthritis Monitoring (DREAM) remission induction cohort were analysed. Both 28-joint counts and more comprehensive joint counts (tender joint count-53, swollen joint count-44) were used.

Results. ACR/EULAR remission was present in 20.1% of the patients when using 28-joint counts and in 17.4% of the patients when applying more comprehensive joint counts. In 108 patients, the PGA score was >1 despite fulfilment of the remaining criteria (TJC28, SJC28 and CRP in mg/dl ≤1). Residual disease activity was observed in 31.5% (34/108) and median (interquartile range) scores on PGA, pain and fatigue were 2.4 (1.8-4.0), 2.0 (1.1-3.0) and 2.7 (1.3-5.0), respectively. Applying more comprehensive joint counts showed comparable results. In 19.5% (100/512) of patients, disease activity was absent (TJC53 = 0, SJC44 = 0, and CRP ≤1). In 41% (n = 41) of these patients, the PGA score was >1. Receiver operating characteristic analysis showed moderate accuracy of the PGA to discriminate between fulfilment and no fulfilment of all remaining criteria.

Conclusion. Frequently, patients did not meet the PGA criterion despite a good clinical disease state. Apparently the PGA is not solely influenced by RA disease activity. In patients with marked divergence between the PGA and objective clinical measurements, caution should be taken when applying the provisional ACR/EULAR definition of remission.

Introduction

The therapeutic goal in RA should be remission (1), which can be generally defined as 'the state of absence of disease activity in patients with a chronic illness, with the possibility of return of disease activity' (2). Remission is associated with less radiological progression and better functional outcome (3).

The ACR and European League Against Rheumatism (EULAR) recently proposed new definitions of remission in RA for clinical trials (4-6). The Boolean-based definition requires a tender joint count (TJC) ≤1, swollen joint count (SJC) ≤1, CRP ≤1 mg/dl and patient global assessment (PGA) ≤1 (on a 0-10 scale) (6).

The PGA asks the patient to give an overall assessment of how the arthritis is doing, thereby integrating a number of dimensions related to RA disease activity. In daily clinical practice it is frequently observed that patients score higher on the PGA than would be expected on the basis of their clinical disease activity (7-9). This assumes that the PGA is not exclusively related to the clinical disease process of RA, in contrast to TJC and SJC and acute-phase response. Therefore, it is disputable whether a PGA score of ≤1 should be a prerequisite for remission.

The purpose of the present study was to apply the provisional ACR/EULAR Boolean-based definition of remission in daily clinical practice and to explore the relation between the PGA remission criterion (≤1) and the patient's clinical disease state.

Patients and methods

Patients

Data were used from the Dutch Rheumatoid Arthritis Monitoring (DREAM) remission induction cohort study, an ongoing multicentre prospective observational cohort study in daily clinical practice in The Netherlands (10). Inclusion criteria were age ≥18 years, a clinical diagnosis of RA, symptom duration (defined as the time from first reported symptom onset to diagnosis of RA) ≤1 year, DAS in 28 joints (DAS-28) ≥2.6 (11), and no prior DMARDs and prednisolone use. Patients were treated according to a treat-to-target strategy aiming at remission (DAS-28 <2.6), with therapy consisting of DMARDs (initial monotherapy, followed by combination therapy), followed by biologic agents in case of persistent disease activity.

This study was approved by the ethical review board of the Medisch Spectrum Twente Hospital and written informed consent was obtained from all patients.

Measures

ACR/EULAR remission

The ACR/EULAR committee has proposed two definitions of remission in RA for clinical trials: a Boolean-based definition and an index-based definition (6). The Boolean-based definition requires fulfilment of four criteria: TJC ≤1, SJC ≤1, CRP ≤1 mg/dl and PGA ≤1 (on a 0-10 scale) at any time point. The index-based definition is defined as a simplified disease activity index (SDAI) ≤3.3 at any time point. As the physician global assessment was not assessed in this cohort, the SDAI could not be calculated.

According to the ACR/EULAR committee, the use of 28-joint counts is sufficient; however, arthritis in joints not included in the 28-joint counts (ankles, feet) will inevitably influence the patient's perception of his/her RA disease activity. It could be expected that a more comprehensive joint assessment is more accurate for the evaluation of remission. Therefore, in this study, ACR/EULAR remission was evaluated using 28-joint counts (TJC28 and SJC28) as well as more comprehensive joint counts (TJC53 and SJC44).

Patient-reported outcomes

For the patient assessment of disease activity (PGA), pain and fatigue, a horizontal 10-cm visual analogue scale (VAS) with scores ranging from 0 (best) to 10 (worst) was used. The wording of questions and anchors were as follows: for the PGA, 'Considering all of the ways your arthritis affects you, mark ''X'' on the scale for how well you are doing' ('very well' to 'very poor'), in accordance with the ACR core set of disease activity measures for RA (12); for pain, 'How much pain did you experience as a result of your arthritis in the past week?' ('no pain at all' to 'unbearable pain'); and for fatigue, 'How fatigued were you as a result of your arthritis in the past week?' ('not fatigued at all' to 'extremely fatigued').

Statistical analyses

In the present study we included patients with a 6-month follow-up assessment enrolled from January 2006 to July 2010. Only observations without missing data in the ACR/ EULAR remission criteria were selected for our analyses. The cohort provided more data on the patient assessment of disease activity and pain than on the patient assessment of fatigue. Descriptive statistics were undertaken to explore the relation between the PGA remission criterion (≤1) and the patient's clinical disease state. Correlations between the patient assessment of disease activity, pain and fatigue were calculated using the Spearman's rank correlation coefficient. The receiver operating characteristic (ROC) curve and the area under the curve (AUC) with S.E. were used to evaluate the ability of the PGA to discriminate between fulfilment of all of the remaining remission criteria (TJC, SJC and

CRP all ≤1) and no fulfilment of all of the remaining remission criteria (at least one >1). The optimal cut-off points were identified by selecting the value showing optimal sensitivity and specificity (13). Statistical analyses were performed using the statistical software package SPSS 18.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

A 6-month follow-up assessment was present in 512 patients with very early RA. Mean (S.D.) age at inclusion was 58.6 (14.3) years, 63.1% (n = 323) of patients were female, median [interquartile range (IQR)] symptom duration was 14 (8-26) weeks, 61.2% (309/505) of patients were RF positive, 58.8% (273/464) had anti-CCP antibodies and mean (S.D.) DAS-28 was 5.0 (1.1).

Prevalence of ACR/EULAR remission

ACR/EULAR remission based on 28-joint counts was observed in 20.1% of patients. When applying the ACR/ EULAR definition using more comprehensive joint counts, remission was observed in 17.4% of patients.

Absence of ACR/EULAR remission

Data for the 409 patients who did not fulfil the ACR/ EULAR remission criteria (based on 28-joint counts) were evaluated. In 158 patients, three of the four criteria were fulfilled. The variable not meeting the remission cut-off point was in 68.4% of PGA, 20.9% of SJC28, 8.2% of CRP and 2.5% of TJC28 (Table 1). When more comprehensive joint counts were used, comparable results were found (Table 1).

Residual disease activity

Residual disease activity not captured by the 28-joint counts was present in 31.5% (34/108) of the patients who had a high PGA score (>1) despite low TJC28 and SJC28 and normal CRP. The use of more stringent criteria allowing no minimal residual disease activity (TJC53 = 0, SJC44 = 0 and normal CRP) showed that of the 100 patients fulfilling these criteria, only 59% (59/100) fulfilled the PGA criterion of ≤1.

Table 1. Fulfilment of the criteria of the provisional ACR/EULAR Boolean-based definition of remission in RA in 512 patients based on 28-joint counts and more comprehensive joint counts.

	ACR/EULAR remission based on TJC28/SJC28 (n = 512)	**ACR/EULAR remission based on TJC53/SJC44 (n = 512)**
Remission	103 (20.1)	89 (17.4)
Non-remission, fewer than three of four criteria fulfilled	251 (49.0)	287 (56.0)
Non-remission, three of four criteria fulfilled	158 (30.9)	136 (26.6)
Variables not fulfilling the criterion of ≤1		
PGA	108/158 (68.4)	80/136 (58.8)
SJC	33/158 (20.9)	34/136 (25.0)
CRP	13/158 (8.2)	10/136 (7.4)
TJC	4/158 (2.5)	12/136 (8.8)

Values are presented as n (%).

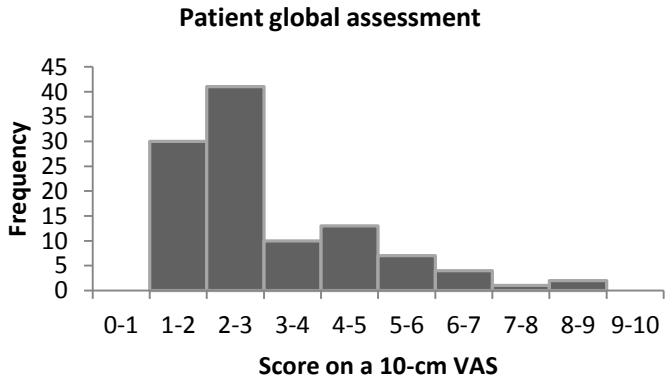
Experience of pain and fatigue

In patients who had a high PGA score (>1) despite low TJC28 and SJC28 and normal CRP, the distribution of the PGA scores showed wide ranges beyond the cut-off point for remission (Fig. 1A). The distributions of the scores on the patient assessment of pain (n = 108) and fatigue (n = 53) are presented in Fig. 1B and C, respectively. These figures show that a considerable number of patients experienced pain and fatigue despite minimal inflammation. The median (IQR) scores for the patient assessment of disease activity, pain and fatigue were 2.4 (1.8-4.0), 2.0 (1.1-3.0) and 2.7 (1.3-5.0), respectively. Overall, the PGA correlated highly with the patient assessment of pain (ρ = 0.820, *P* = 0.000) and moderately with fatigue (ρ = 0.528, *P* = 0.000).

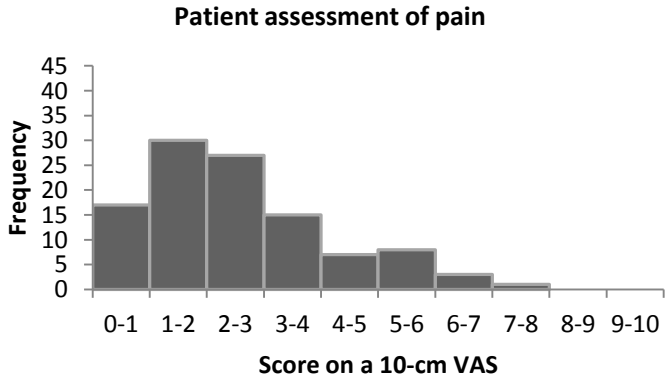
Discriminative ability of the PGA

The ROC curve analysis showed moderate accuracy of the PGA to discriminate between the fulfilment of the TJC28, SJC28 and CRP remission criteria vs no fulfilment of all three remaining criteria (at least one >1), with an AUC (S.E.) of 0.73 (0.02). The optimal cut-off point of PGA in differentiating the two conditions was estimated at 2 (74% sensitivity and 65% specificity). When applying more comprehensive joint counts, comparable results were found (data not shown).

A



B



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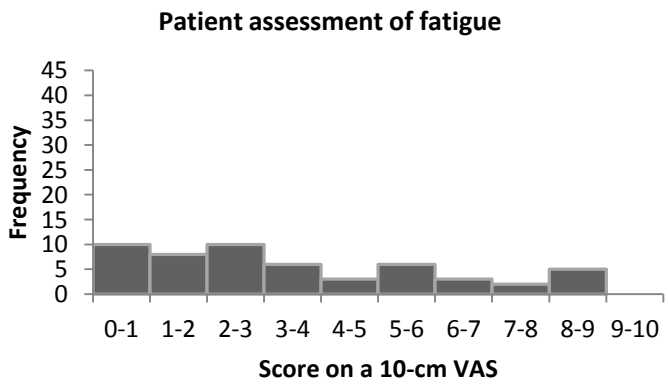

Figure 1. Distribution of (A) the patient assessment of disease activity (PGA) (n = 108), (B) pain (n = 108) and (C) fatigue (n = 53) on a 0-10 VAS in 108 patients who did not meet the PGA criterion of ≤1 of the provisional ACR/EULAR Boolean-based definition of remission in RA, despite TJC28, SJC28 and CRP meeting the cut-off point of remission (≤1).

Discussion

The present study demonstrated that RA patients regularly do not meet the PGA criterion (≤1) of the provisional ACR/EULAR Boolean-based definition of remission in RA, despite a good clinical disease state. This finding was not fully explained by residual disease activity. Pain and fatigue were experienced by a considerable number of patients despite minimal inflammation. Moreover, the accuracy of the PGA to discriminate between fulfilment and no fulfilment of all of the remaining three remission criteria was moderate. Apparently other factors can drive non-remission of the PGA criterion in the absence of evidence of joint inflammation in RA. Patient-reported outcomes (PROs) have been increasingly recognized as important and are now part of the core set of disease activity measures (12). The use of PROs in defining remission assumes a strict relation with objective clinical disease activity parameters. Kievit *et al.* (14) have shown that the patient's perception of health can be different with equal disease activity, depending on the moment in the disease course. Furthermore, patients with RA often suffer from pain, physical disability, fatigue (15) and symptoms of depression and anxiety due to significant comorbidities, which may influence the patient's perception of how the arthritis is doing (16). Additionally, in RA patients with concomitant FM, the low threshold of pain sensitivity found in this disease may lead to overestimation of the PGA (17). Social, cultural and ethnic factors (18-20) as well as the clinical setting (clinical trial or daily clinical practice) may also play a role in the reporting of disease activity.

Some remarks on the present study should be addressed. We used data from an observational cohort study in daily clinical practice. However, the provisional ACR/EULAR definition of remission was defined for trial settings. The ACR/EULAR committee suggested a different definition for clinical-based practice that does not require an acute-phase reactant (i.e. TJC ≤1, SJC ≤1 and PGA ≤1), since this is frequently not immediately available in the clinical setting. Obviously the definition that was formulated for clinical practice settings also encounters the problem regarding the PGA, and thus applying this definition would not affect our results.

We acknowledge further research is needed to formally test whether the PGA criterion in its present form or a modification adds discriminatory power over and above that provided by the TJC, SJC and CRP in discriminating between patients with and without clinically relevant radiological progression in trial and observational datasets.

In conclusion, this exploratory study demonstrated that the PGA criterion of the provisional ACR/EULAR Boolean-based definition of remission in RA has limitations in daily clinical practice, because patients that are obviously in clinical remission can score high on the PGA due to other reasons than their RA disease activity. Caution should be taken in

patients with marked divergence between subjective and objective clinical measurements when applying the definition.

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References

1. Smolen JS, Landewe R, Breedveld FC, Dougados M, Emery P, Gaujoux-Viala C, 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. Remission. http://en.wikipedia.org/wiki/Remission (24 January 2011, date last accessed).
3. van Tuyl LH, Felson DT, Wells G, Smolen J, Zhang B, Boers M**.** Evidence for predictive validity of remission on long-term outcome in rheumatoid arthritis: a systematic review. Arthritis Care Res (Hoboken). 2010;62:108-17.
4. van Tuyl LH, Vlad SC, Felson DT, Wells G, Boers M**.** Defining remission in rheumatoid arthritis: results of an initial American College of Rheumatology/European League Against Rheumatism consensus conference. Arthritis Rheum. 2009;61:704-10.
5. Boers M, Felson DT, Wells G, van Tuyl LH, Zhang B, Funovits J, et al. Progress toward the development of a new definition of remission in rheumatoid arthritis. Bull NYU Hosp Jt Dis. 2010;68:140-2.
6. Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LH, Funovits J, et al. American college of rheumatology/european league against rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Ann Rheum Dis. 2011;70:404-13.
7. Suarez-Almazor ME, Conner-Spady B, Kendall CJ, Russell AS, Skeith K**.** Lack of congruence in the ratings of patients' health status by patients and their physicians. Med Decis Making. 2001;21:113-21.
8. Nicolau G, Yogui MM, Vallochi TL, Gianini RJ, Laurindo IM, Novaes GS**.** Sources of discrepancy in patient and physician global assessments of rheumatoid arthritis disease activity. J Rheumatol. 2004;31:1293-6.
9. Barton JL, Imboden J, Graf J, Glidden D, Yelin EH, Schillinger D**.** Patient-physician discordance in assessments of global disease severity in rheumatoid arthritis. Arthritis Care Res (Hoboken). 2010;62:857-64.
10. Vermeer M, Kuper HH, Hoekstra M et al. Implementation of a treat-to-target strategy in very early rheumatoid arthritis: results of the Dutch Rheumatoid Arthritis Monitoring remission induction cohort study. Arthritis Rheum 2011;63:2865-72.
11. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL**.** 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.

12. Felson DT, Anderson JJ, Boers M, Bombardier C, Chernoff M, Fried B, et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. The Committee on Outcome Measures in Rheumatoid Arthritis Clinical Trials. Arthritis Rheum. 1993;36:729-40.
13. Perkins NJ, Schisterman EF**.** The inconsistency of "optimal" cutpoints obtained using two criteria based on the receiver operating characteristic curve. Am J Epidemiol. 2006;163:670-5.
14. Kievit W, Welsing PM, Adang EM, Eijsbouts AM, Krabbe PF, van Riel PL**.** Comment on the use of self-reporting instruments to assess patients with rheumatoid arthritis: the longitudinal association between the DAS28 and the VAS general health. Arthritis Rheum. 2006;55:745-50.
15. Wolfe F, Hawley DJ, Wilson K**.** The prevalence and meaning of fatigue in rheumatic disease. J Rheumatol. 1996;23:1407-17.
16. Radner H, Smolen JS, Aletaha D**.** Comorbidity affects all domains of physical function and quality of life in patients with rheumatoid arthritis. Rheumatology (Oxford). 2011;50:381-8.
17. Toms J, Soukup T, Bradna P, Hrncir Z**.** Disease activity composite indices in patients with rheumatoid arthritis and concomitant fibromyalgia. J Rheumatol. 2010;37:468; author reply 9.
18. Vlaar AP, ten Klooster PM, Taal E, Gheith RE, El-Garf AK, Rasker JJ, et al. A cross-cultural study of pain intensity in Egyptian and Dutch women with rheumatoid arthritis. J Pain. 2007;8:730-6.
19. Yazici Y, Kautiainen H, Sokka T**.** Differences in clinical status measures in different ethnic/racial groups with early rheumatoid arthritis: implications for interpretation of clinical trial data. J Rheumatol. 2007;34:311-5.
20. Celik S, Fresko I, Sut N, Batumlu NM, Yazici H, Yazici Y**.** Differences in pain and fatigue perception among a group of rheumatoid arthritis patients in the United States and in Turkey who have similar disease activity and functional status. Clin Exp Rheumatol. 2010;28:884-7.

Chapter 8 |

Summary and general discussion

Summary

Clinical trials have shown that a treat-to-target (T2T) approach is effective in lowering disease activity and, ultimately, in reaching remission in early rheumatoid arthritis (RA). The question remained whether these beneficial results could be translated into daily clinical practice. The objective of this thesis was to explore the effects of implementing a T2T strategy aiming at remission in early RA. For this purpose, we started the Dutch Rheumatoid Arthritis Monitoring (DREAM) remission induction cohort, the results of which are presented in this thesis.

Chapter 2 presents the one year results of a T2T strategy aiming at remission (defined as a Disease Activity Score in 28 joints (DAS28) < 2.6 (1)). After six and twelve months of follow-up, the percentages of patients in remission were high (i.e. 47% and 58%, respectively). Moreover, remission was achieved rapidly. Preliminary results on radiographic outcomes showed that radiographic damage was limited and that the majority of patients did not have clinically relevant radiographic progression. Optimal use of methotrexate (MTX) (monotherapy followed by combination therapy with other conventional disease-modifying antirheumatic drugs (DMARDs) when indicated) proved to be successful in achieving the treatment goal. Only 10% of patients needed an anti-tumor necrosis factor α (anti-TNF) agent to improve disease activity in the first year. This study showed that a T2T strategy in combination with per-protocol treatment is feasible and successful for attaining remission in very early RA. Moreover, remission was proven to be a realistic goal for daily clinical practice.

Chapter 3 aims to answer the question whether a tightly controlled treatment strategy aiming at remission (i.e. T2T) is more effective than usual care treatment for reaching remission after one year in early RA patients. For this purpose, two strategies derived from two early RA inception cohorts from two different regions including patients who fulfilled the American College of Rheumatology (ACR) classification criteria for RA (2) were compared. Patients in the tight control group were treated according to a T2T strategy aiming at remission (DREAM remission induction cohort). Patients in the usual care group were treated at the discretion of the rheumatologists, without DAS28-guided treatment decisions. After one year, remission had been achieved more frequently and rapidly in the tight control group than in the usual care group, with remission percentages of 55% versus 30%, respectively. Concordantly, T2T resulted in a larger decrease in DAS28, with a larger proportion of patients having low disease activity, and greater improvements in functional ability and patient's assessments of pain and general health. In both groups, a step-up strategy had most commonly been applied and the numbers of patients receiving anti-TNF

therapy during follow-up was comparable. The main differences in treatment strategies between the groups were that in the tight control group nearly all patients started with MTX, while starting with MTX was delayed in the usual care group, and that combination therapy was more frequently used in the tight control group. According to the results of this study, a T2T strategy aiming at remission may lead to a greater proportion of patients attaining remission more rapidly than treatment according to usual care in early RA.

Chapter 4 investigates whether the improved clinical outcomes of a T2T strategy aiming at remission which were achieved early in the course of the disease, as demonstrated in the previous chapters, are sustained in the long-term. Here, we present the three year results of T2T, with respect to (sustained) remission, radiographic progression, physical function, and health-related quality of life. After three years, the majority of patients was in remission (i.e. 62%). Sustained remission (defined as ≥ six months) was observed at least once during the first three years of follow-up in 71% of patients, which in the majority of these was achieved with conventional DMARDs only. In line with the favorable results on disease activity, physical function and health-related quality of life also demonstrated significant improvements over the first six months of follow-up, after which the results remained stable. Radiographic damage and progression were extremely low, even after three years of follow-up. This study has shown that the initial beneficial outcomes of T2T are sustained in the long-term, with high (sustained) remission rates, improved physical function and health-related quality of life, and limited radiographic damage after three year.

Chapter 5 aims to evaluate adherence to the T2T recommendations. We examined whether the recommendations resulted in regular assessment of the disease activity using DAS28 and whether medication was adapted according to the treatment advice (i.e. medication protocol). Furthermore, we explored possible reasons for non-adherence to the T2T recommendations. Results show that the DAS28 was measured at nearly all cohort visits and that adherence to the treatment advice was observed in the majority of visits (i.e. 69%). In case of non-adherence, valid arguments for deviating from the recommendations were observed in the majority of cases. The main reason for non-adherence was discordance between disease activity status according to the rheumatologist or to the DAS28. At 69%, adherence to the T2T recommendations was probably optimal, as striving for 100% adherence is not realistic because treatment of patients is subject to side effects and comorbidities. This study showed that implementation of T2T is feasible in daily clinical practice.

Chapter 6 presents the results of a cost-effectiveness and cost-utility analysis of a T2T strategy aiming at remission, compared to usual care for the treatment of early RA patients in daily clinical practice over a period of up to three years. The concept of T2T assumes that intensive effort and costs are made at the beginning of the disease, to gain health and cost savings later. The question was whether these health benefits outweigh the extra costs associated with T2T. For this purpose, the same comparison was used as was described in chapter 3. This study demonstrated that T2T is more effective than usual care, i.e. with higher remission percentages and a larger gain in quality adjusted life years (QALYs). The incremental cost effectiveness ratio (ICER) was € 3,591 per patient in remission after two years and T2T was dominant after three years. The incremental cost utility ratio (ICER) was € 19,410 per QALY after two years and T2T was dominant after three years. Over the first two years of treatment, T2T was associated with higher costs but also with substantial higher effectiveness, compared with usual care. In the third year, T2T probably becomes cost-saving. According to these results, T2T is the preferred strategy over usual care. The drivers of absolute costs and cost differences between T2T and usual care were anti-TNF therapy and hospitalization. The conclusion of the present study was that T2T is cost-effective.

Chapter 7 discusses the patient global assessment (PGA) remission criterion of the recently introduced provisional ACR/European League Against Rheumatism (EULAR) Boolean-based definition of remission in RA (3). This definition requires a tender joint count ≤ 1, swollen joint count ≤ 1, C-reactive protein ≤ 1 mg/dl and patient global assessment (PGA) ≤ 1 (on a 0-10 scale). In daily clinical practice, it has frequently been observed that patients score higher on the PGA than would be expected on basis of their clinical disease activity. This suggests that the PGA is not exclusively related to the clinical disease process of RA, and it is therefore disputable whether a PGA score of ≤ 1 should be used as a prerequisite for remission. In the present study we explored the relation between the PGA remission criterion and the patient's clinical disease state. We indeed observed that patients regularly do not meet the PGA criterion, despite a good clinical disease state. Apparently, other factors may drive non-remission of the PGA criterion in the absence of evident joint inflammation in RA. This study demonstrated that the PGA criterion of the provisional ACR/EULAR definition of remission in RA has limitations in daily clinical practice.

General discussion

RA is a chronic disease which can have a progressive course. Since cure of the disease is not possible with the currently available treatment options, achieving and sustaining a

state of clinical remission is the current appropriate treatment goal, in order to prevent radiographic damage and functional disability.

Window of opportunity

It is widely accepted that RA should be treated as soon as possible – the earlier, the better – since early initiation of treatment has proven superiority with regard to clinical outcomes over a delayed start of treatment. The concept of a "therapeutic window of opportunity" has been hypothesized, which assumes the existence of a period of time in which the immune-driven inflammatory process is more susceptible to treatment than at later stages of the disease. In this early phase, treatment may have the potential to alter the disease process, thereby preventing eventual joint destruction (4,5). Many patients respond well to conventional DMARDs in this phase (6,7), with levels of effectiveness approaching or even exceeding those obtained with biologic agents (5). There is some indication that after an excellent early response has been achieved, combination therapy may successfully be withdrawn without causing disease relapse, at least in some patients (8,9).

If such a window of opportunity exists, it is of utmost importance to diagnose RA as soon as possible. However, diagnosis of RA in the very early stages of the disease is difficult. In patients with recent-onset arthritis, RA may develop in some, whereas in others the arthritis remits spontaneously, remains undifferentiated, or develops into other rheumatic diseases (10). Anti-cyclic citrullinated peptide (anti-CCP) antibodies can sometimes be detected several years before clinical symptoms develop (2) and are thus important predictors of the development of RA (11). The PRObable RA: Methotrexate versus Placebo Treatment (PROMPT) study has demonstrated that treatment with MTX can postpone the progression to RA in patients with undifferentiated arthritis who have anti-CCP antibodies, but it cannot prevent it (12). Notably, as yet there is no formal definition of early RA. Other studies in so-called early RA permitted disease durations up to one to two years after the diagnosis to define early disease. However, the duration of the disease extends back to the onset of symptoms, or even before that, and not just to the time of diagnosis. The RA population presented in this thesis is referred to as 'very early RA' as patients had a duration of symptoms of one year or less and treatment was initiated immediately after diagnosis. Obviously, general practitioners should be aware of the importance of early referral of patients with symptoms of arthritis to the rheumatologist, thereby making early diagnosis possible.

Optimal drug treatment

MTX is often chosen as initial treatment and as an anchor drug in combination therapies due to its high effectiveness and low side effects profile (13). MTX was first introduced in the "start low and go slow" era of RA; a common empirical approach was to start with a dose of 7.5 mg/week, which was then slowly increased over several months to a maximum of 15 mg/week. Clinical trials with biologic agents have changed the way MTX is used in practice by demonstrating that higher dosages are more effective (14). Although dosages of up to 20 mg/week (where indicated) have been used in pivotal randomized clinical trials, in clinical practice dosages up to 25-35 mg/week are believed to be effective and safe. Moreover, there appears to be a dose-effect relation over the full MTX dose range. In general, this thesis shows that immediate initiation of MTX at a starting dose of 15 mg/week and reaching a dose of 25 mg/week early in the course of the disease leads to an excellent response in the majority of patients. These findings are consistent with the results of the Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA) study, which demonstrated that intensified treatment with MTX using a tight control approach substantially enhances the clinical efficacy in the very early phase of the disease (7). In case of a suboptimal response to MTX, sulfasalazine (SSZ) was added to the medication. Combination DMARD therapy is widely used and effective as initial therapeutic strategy or after monotherapy has failed. Results of the Combinatietherapie Bij Reumatoïde Artritis (COBRA) trial showed that intensive combination therapy with MTX, SSZ and prednisolone is more effective than SSZ alone (15). Moreover, O'Dell *et al.* demonstrated that triple therapy with MTX, SSZ and hydroxychloroquine has superiority over MTX alone (16). Although generally the combination of MTX and SSZ shows good response, results on the efficacy of the combination of MTX and SSZ versus either drug alone have not been consistent in the literature (17-20). This thesis demonstrates that the majority of patients in daily clinical practice can achieve (sustained) remission with intensive treatment with conventional DMARDs (monotherapy or combination therapy) (see chapter 2-4). This underscores the importance of aiming at the target of remission, using whatever drugs it takes, as long as safety is guaranteed.

The value of anti-TNF agents (or biologics), either as monotherapy or in combination with MTX, has been proven in many industry-driven clinical trials in early RA. There is evidence that anti-TNF therapy is more effective than DMARDs alone (14,21) or in combination therapy (9). Remarkably, in the studies presented in this thesis, anti-TNF therapy was prescribed for only a minority of the patients. As anti-TNF therapy is associated with substantial higher costs, overtreatment with these agents should be prevented. In the T2T strategy of the DREAM remission induction cohort, the first anti-TNF agent was already allowed to be prescribed after 24 weeks, but only for those patients

who had at least moderate disease activity and who had failed on at least two conventional DMARDs including MTX at an optimal dose. Moreover, as soon as sustained remission was achieved, therapy was tapered and eventually discontinued. Evidently, prescribing anti-TNF or biologic agents is not a necessity in all patients. From the health economic perspective, it seems correct to limit the prescription of anti-TNF agents until after failure of T2T administration of MTX and combinations of DMARDs. This emphasizes the appropriateness of the guideline of the Dutch Society for Rheumatology on the use of anti-TNF agents after failure of DMARDs (22).

Treat-to-target

Over the last decade, treatment strategies including T2T principles have been applied increasingly. The successful implementation of a T2T strategy aiming at remission as illustrated in this thesis indicates that T2T is feasible and effective in early RA patients in daily clinical practice. To treat the disease to target, it is evident that a valid target should be set. It is widely accepted that remission should now be the therapeutic goal in RA. Remission can generally be defined as "the state of absence of disease activity in patients with a chronic illness, with the possibility of return of disease activity" (23). Unfortunately, there is no clear and universal definition of remission. Remission is generally considered to be the absence of disease activity as measured by tender and swollen joint counts and acute phase responses. The patient's assessment of disease activity is also often included in remission criteria. However, the patient's assessment may incorporate much more than just disease activity, such as pain, physical disability, fatigue and symptoms of depression and anxiety due to significant comorbidities. Notwithstanding the importance of patient reported outcomes in health care, especially in the management of RA, caution should be taken when using the patient's perspective of disease activity to define remission when this is the target for treatment (24). For example, the recently introduced Boolean-based version of the provisional ACR/EULAR definition of remission in RA (3) has been criticized in this thesis (see chapter 7) and in other studies (25-27), because it places too much emphasis on the patient's perspective.

In this thesis, the target was remission according to the DAS28. Because the DAS28 is a continuous measure, it enables evaluation of how close to the target a patient has progressed, in contrast to dichotomous measures of remission. However, the remission cut-off point of the DAS28 has been subject to criticism. Because synovitis may be present in joints not included in the 28 joint count (e.g. the feet), patients with DAS28 remission may still have residual disease activity (28,29). The DAS28 remission criterion is less stringent than that of, for example, the original Disease Activity Score (DAS) (30) or the ACR remission criteria (31), and allows several swollen and/or tender joints to be

present (28). The shortcomings of a particular instrument used to assess remission should be understood. As the results presented in this thesis appeared robust and independent from the various definitions of remission, it may be assumed that the target of remission can be defined using any of the available definitions. Treating to a target of remission is more important than the exact definition of remission.

The feasibility of T2T in daily clinical practice depends on several factors. Prior to the implementation of T2T, consensus should be reached on the therapeutic regimen, frequency of monitoring disease activity and the definition of the target by all the rheumatologists concerned. It has been suggested that tight control with protocolised treatment adjustments is more beneficial than tight control without a protocol (32), probably because medication is changed more often if the changes are imposed by a protocol. Evidently, treatment protocols reflect national guidelines and local reimbursement regulations.

The implementation of T2T is a challenge for rheumatologists as well as their patients, as it involves several logistical aspects. The routine use of measures of disease activity has received objection from rheumatologists (33). Especially the measurement of the number of swollen and tender joints is often judged to be difficult and time-consuming (34). Some composite indices are also complex to calculate. The DAS28 for example involves a complex mathematical formula requiring additional tools such as a DAS-calculator. It is therefore important to be familiar with the instrument. The reallocation of the measurement of disease activity to a trained rheumatology nurse may play a substantial role in the successful implementation of DAS28-driven treatment (35). In the DREAM remission induction cohort, DAS28 was usually evaluated by a nurse prior to the visit to the rheumatologist, and therefore the T2T approach did not require a lot of extra effort and time for the rheumatologist during the clinical visit.

The logistics and data collection may be facilitated by information and communication technology, for the physicians as well as the patients. The web-based Rheumatology Online Monitoring Application (ROMA) was developed to prospectively gather data on patient characteristics, medication, clinical and laboratory measures and questionnaires in a standardized way in an electronic database. Patients were invited to fill out the questionnaires (e.g. the Health Assessment Questionnaire and the 36-item Short Form Health Survey) prior to their clinical consultation, either on touch-screen computers which were present at the clinic or through the ROMA-website accessible using a personal login account. The logistic process was supported further, as the data were immediately available to the physician at the time of the clinical consultation, thereby providing relevant and up-to-date information on the patient's status.

The feasibility of T2T does not only depend on the physicians but also on the patients. Until the desired target is reached, drug treatment should be adjusted by frequent and strict monitoring. However, patients might be reluctant to change medications frequently and might fear side effects. Therefore, patients should be well informed and motivated about the T2T concept and its potential benefits. Obviously, T2T can be applied with adjustments as required for the needs and safety of the individual patient. We considered the adherence to the T2T recommendations as presented in this thesis to be optimal (see chapter 5).

Although the implementation of a T2T strategy aiming at remission is an expensive effort, it will pay off in the long-term through more beneficial clinical outcomes for the patients, and eventually it will probably save costs (see chapter 6). Therefore, it is expected that T2T is cost-effective, and probably cost-saving in the longer-term.

The value of observational data

The translation of beneficial results from clinical trials to daily clinical practice is considered to be a challenge (36). This is demonstrated by the fact that the concept of T2T has not been fully implemented in all rheumatology clinics, despite solid evidence of its efficacy from randomized controlled trials (RCTs). The key distinguishing feature of a RCT is that study participants, after assessment of eligibility and recruitment, are randomly allocated to an intervention group or a control group. This reduces selection bias. Moreover, confounding factors can be accounted for in the design of the study itself. This leads to high internal validity. Moreover, RCTs may provide information on the cause and effect relationship between an intervention and its outcome. Therefore, RCTs are a superior methodology in the hierarchy of evidence in therapy. However, the extent to which the results of RCTs are applicable outside the RCT varies; that is, external validity may be limited. This may be due to the controlled setting and stringent inclusion and exclusion criteria (37). Therefore, the generalizability of the results of RCTs to daily clinical practice is often limited (38,39). The question is whether the results of RCTs hold true in the 'real-world' of RA care in daily clinical practice, as daily practice is characterized by a more heterogeneous patient population (40), variation in prescription behavior of physicians (41,42), and restrictions in time, costs and resources.

Observational data from registries and cohort studies may provide important additional information to RCTs alone regarding not only drug safety but also the effectiveness, use and cost-effectiveness of treatment strategies in the real-world (43). Observational studies differ from standard RCTs in that they involve the collection of observational data on study participants over an extended period of time without focusing on a specific comparison of intervention versus control groups. These studies have

inherent limitations in terms of their susceptibility to bias and confounding, restricting their ability to define causality and focusing more on establishing association. However, their strengths include reflecting daily clinical practice more closely than RCTs, both in terms of the heterogeneous patient populations that are included (i.e. less strictly selected) and their medical interventions. Therefore, the results of observational studies can be more easily generalized to the entire population of patients. Moreover, observational studies usually include a much larger number of patients and have a longer follow-up period than RCTs. Health economic evaluations using observational data are valuable for making proper decisions regarding coverage and reimbursement (43), as often modeling techniques with many underlying assumptions and uncertainties are used.

This thesis shows that the beneficial results of clinical trials applying T2T can indeed be translated into daily clinical practice. The studies in the DREAM registry and ROMA provide important sources of data to bridge the gap between evidence-based medicine and daily clinical practice.

Future directions

We would like to propose several possible directions for future research. Future research should focus on the long-term efficacy of T2T aiming at remission, safety and performance in early RA patients, beyond three years of follow-up. RA is a chronic disease and therefore three years of follow-up does not fully capture the significant burden of disease. Long-term data are critical for determining how many patients will remain in sustained remission and how many may reduce and eventually discontinue medication. This could show whether sustained drug-free remission is an achievable goal in daily clinical practice. Also, the long-term results regarding radiographic outcome are of high value, in order to evaluate whether intensive treatment with conventional DMARDs prevents long-term radiographic damage and whether sustained remission leads to 'radiographic remission'.

Several therapeutic regimes and treatment approaches have been introduced over the last decade, but the most optimal strategy for patients newly diagnosed with RA remains undecided. The results described in this thesis reflect the effects of only one medication strategy; no comparator was included. Therefore, the question remains what the most effective treatment strategy regarding medication is in early RA, and other strategies will be evaluated in forthcoming cohorts. While the majority of patients were in remission after three years of follow-up, there were still patients who had not been able to reach (sustained) remission. Remission might not be a realistic goal for all patients, and an acceptable alternative therapeutic goal may be low disease activity (44). Still almost 20% of patients retained moderate or high disease activity. When these patients had cycled through the whole medication protocol, the attending rheumatologist was free to

determine the next treatment steps. This raises the question for future research of what would be an appropriate strategy for these patients. Furthermore, predictors for achieving (sustained) remission should be explored.

Finally, the (cost-)effectiveness of implementing a T2T strategy aiming at remission in early RA should be validated in other study populations.

Conclusions

The implementation of a T2T strategy aiming at DAS28 remission results in beneficial clinical outcomes in very early RA. Since T2T has been shown to be feasible in daily clinical practice, such treatment approaches should be embraced to optimize clinical outcomes for patients with early RA in order to improve their health-related quality of life. Remission has proven to be a realistic goal in daily clinical practice, and therefore, remission should be the mission for all patients.

References

1. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL**.** 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. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988;31:315-24.
3. Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LH, Funovits J, et al. American college of rheumatology/european league against rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Ann Rheum Dis. 2011;70:404-13.
4. Quinn MA, Conaghan PG, Emery P**.** The therapeutic approach of early intervention for rheumatoid arthritis: what is the evidence? Rheumatology (Oxford). 2001;40:1211-20.
5. Nell VP, Machold KP, Eberl G, Stamm TA, Uffmann M, Smolen JS**.** 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.
6. Anderson JJ, Wells G, Verhoeven AC, Felson DT**.** Factors predicting response to treatment in rheumatoid arthritis: the importance of disease duration. Arthritis Rheum. 2000;43:22-9.
7. Verstappen SM, Jacobs JW, van der Veen MJ, Heurkens AH, Schenk Y, ter Borg EJ, 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.
8. Quinn MA, Conaghan PG, O'Connor PJ, Karim Z, Greenstein A, Brown A, et al. Very early treatment with infliximab in addition to methotrexate in early, poor-prognosis rheumatoid arthritis reduces magnetic resonance imaging evidence of synovitis and damage, with sustained benefit after infliximab withdrawal: results from a twelve-month randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2005;52:27-35.
9. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJ, Hazes JM, 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.
10. van Aken J, van Dongen H, le Cessie S, Allaart CF, Breedveld FC, Huizinga TW**.** Comparison of long term outcome of patients with rheumatoid arthritis presenting

with undifferentiated arthritis or with rheumatoid arthritis: an observational cohort study. Ann Rheum Dis. 2006;65:20-5.
11. van Gaalen FA, Linn-Rasker SP, van Venrooij WJ, de Jong BA, Breedveld FC, Verweij CL, et al. Autoantibodies to cyclic citrullinated peptides predict progression to rheumatoid arthritis in patients with undifferentiated arthritis: a prospective cohort study. Arthritis Rheum. 2004;50:709-15.
12. van Dongen H, van Aken J, Lard LR, Visser K, Ronday HK, Hulsmans HM, et al. Efficacy of methotrexate treatment in patients with probable rheumatoid arthritis: a double-blind, randomized, placebo-controlled trial. Arthritis Rheum. 2007;56:1424-32.
13. Pincus T, Yazici Y, Sokka T, Aletaha D, Smolen JS**.** Methotrexate as the "anchor drug" for the treatment of early rheumatoid arthritis. Clin Exp Rheumatol. 2003;21(5 Suppl 31):S179-85.
14. Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, Keystone EC, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. N Engl J Med. 2000;343:1586-93.
15. Boers M, Verhoeven AC, Markusse HM, van de Laar MA, Westhovens R, van Denderen JC, et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet. 1997;350:309-18.
16. O'Dell JR, Haire CE, Erikson N, Drymalski W, Palmer W, Eckhoff PJ, et al. Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications. N Engl J Med. 1996;334:1287-91.
17. van der Kooij SM, de Vries-Bouwstra JK, Goekoop-Ruiterman YP, van Zeben D, Kerstens PJ, Gerards AH, et al. Limited efficacy of conventional DMARDs after initial methotrexate failure in patients with recent onset rheumatoid arthritis treated according to the disease activity score. Ann Rheum Dis. 2007;66:1356-62.
18. Capell HA, Madhok R, Porter DR, Munro RA, McInnes IB, Hunter JA, 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.
19. Haagsma CJ, van Riel PL, de Jong AJ, van de Putte LB**.** Combination of sulphasalazine and methotrexate versus the single components in early rheumatoid arthritis: a randomized, controlled, double-blind, 52 week clinical trial. Br J Rheumatol. 1997;36:1082-8.

20. Schipper LG, Fransen J, Barrera P, Van Riel PL. Methotrexate in combination with sulfasalazine is more effective in rheumatoid arthritis patients who failed sulfasalazine than in patients naive to both drugs. Rheumatology (Oxford). 2009;48:828-33.
21. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum. 2006;54:26-37.
22. Dutch Society for Rheumatology. Richtlijnen. Medicijnen: Het toepassen van TNF-blokadde in de behandeling van reumatoïde artritis. Haarlem: DC//HG; 2003.
23. Remission. http://en.wikipedia.org/wiki/Remission (24 January 2011, date last accessed).
24. Westhovens R, Verschueren P. Rheumatoid arthritis: Defining remission in patients with RA in clinical practice. Nat Rev Rheumatol. 2012;8:445-7.
25. Studenic P, Smolen JS, Aletaha D. Near misses of ACR/EULAR criteria for remission: effects of patient global assessment in Boolean and index-based definitions. Ann Rheum Dis. 2012;71:1702-5.
26. Masri KR, Shaver TS, Shahouri SH, Wang S, Anderson JD, Busch RE, et al. Validity and Reliability Problems with Patient Global as a Component of the ACR/EULAR Remission Criteria as Used in Clinical Practice. J Rheumatol. 2012;39:1139-45.
27. Kuriya B, Sun Y, Boire G, Haraoui B, Hitchon C, Pope JE, et al. Remission in Early Rheumatoid Arthritis -- A Comparison of New ACR/EULAR Remission Criteria to Established Criteria. J Rheumatol. 2012;39:1155-8.
28. Landewe R, van der Heijde D, van der Linden S, Boers M. 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.
29. Bakker MF, Jacobs JW, Kruize AA, van der Veen MJ, van Booma-Frankfort C, Vreugdenhil SA, et al. Misclassification of disease activity when assessing individual patients with early rheumatoid arthritis using disease activity indices that do not include joints of feet. Ann Rheum Dis. 2012;71:830-5.
30. van der Heijde DM, van 't Hof M, van Riel PL, van de Putte LB. Development of a disease activity score based on judgment in clinical practice by rheumatologists. J Rheumatol. 1993;20:579-81.
31. Pinals RS, Masi AT, Larsen RA. Preliminary criteria for clinical remission in rheumatoid arthritis. Arthritis Rheum. 1981;24:1308-15.

32. Schipper LG, van Hulst LT, Grol R, van Riel PL, Hulscher ME, Fransen J**.** 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.
33. Haraoui B, Smolen JS, Aletaha D, Breedveld FC, Burmester G, Codreanu C, et al. Treating Rheumatoid Arthritis to Target: multinational recommendations assessment questionnaire. Ann Rheum Dis. 2011;70:1999-2002.
34. Pincus T**.** Limitations of a quantitative swollen and tender joint count to assess and monitor patients with rheumatoid arthritis. Bull NYU Hosp Jt Dis. 2008;66:216-23.
35. van Hulst LT, Creemers MC, Fransen J, Li LC, Grol R, Hulscher ME, et al. How to improve DAS28 use in daily clinical practice?--a pilot study of a nurse-led intervention. Rheumatology (Oxford). 2010;49:741-8.
36. Verschueren P, Westhovens R**.** Optimal care for early RA patients: the challenge of translating scientific data into clinical practice. Rheumatology (Oxford). 2011;50:1194-200.
37. Wolfe F, Michaud K, Dewitt EM**.** Why results of clinical trials and observational studies of antitumour necrosis factor (anti-TNF) therapy differ: methodological and interpretive issues. Ann Rheum Dis. 2004;63 Suppl 2:ii13-ii7.
38. Zink A, Strangfeld A, Schneider M, Herzer P, Hierse F, Stoyanova-Scholz M, et al. Effectiveness of tumor necrosis factor inhibitors in rheumatoid arthritis in an observational cohort study: comparison of patients according to their eligibility for major randomized clinical trials. Arthritis Rheum. 2006;54:3399-407.
39. Kievit W, Fransen J, Oerlemans AJ, Kuper HH, van der Laar MA, de Rooij DJ, et al. The efficacy of anti-TNF in rheumatoid arthritis, a comparison between randomised controlled trials and clinical practice. Ann Rheum Dis. 2007;66:1473-8.
40. Sokka T, Pincus T**.** Most patients receiving routine care for rheumatoid arthritis in 2001 did not meet inclusion criteria for most recent clinical trials or american college of rheumatology criteria for remission. J Rheumatol. 2003;30:1138-46.
41. Hoekstra M, van de Laar MA, Bernelot Moens HJ, Kruijsen MW, Haagsma CJ**.** Longterm observational study of methotrexate use in a Dutch cohort of 1022 patients with rheumatoid arthritis. J Rheumatol. 2003;30:2325-9.
42. Harrold LR, Harrington JT, Curtis JR, Furst DE, Bentley MJ, Shan Y, et al. Prescribing practices in a US cohort of rheumatoid arthritis patients before and after publication of the American College of Rheumatology treatment recommendations. Arthritis Rheum. 2012;64:630-8.
43. van Vollenhoven RF, Severens JL**.** Observational studies: a valuable source for data on the true value of RA therapies. Clin Rheumatol. 2011;30 Suppl 1:S19-24.

44. Smolen JS, Aletaha D, Bijlsma JW, Breedveld FC, Boumpas D, Burmester G, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis. 2010;69:631-7.

Samenvatting
(Summary in Dutch)

In **hoofdstuk 1** werd beschreven dat reumatoïde artritis (RA) een chronische ziekte is die wordt gekenmerkt door ontstekingen in de gewrichten en dat het snel tot rust brengen van de ontstekingen essentieel is voor een goede prognose. Daarom is het doel van de behandeling het bereiken van remissie in een zo vroeg mogelijk stadium van de ziekte. Meerdere klinische trials hebben laten zien dat het frequent meten van de ziekteactiviteit en het streven naar een van tevoren bepaalde mate van ziekteactiviteit (bijvoorbeeld remissie) een goede aanpak is om patiënten met recent gediagnosticeerde RA te behandelen. Indien de ziekteactiviteit op een bepaald meetmoment te hoog is moet vervolgens direct de medicatie worden aangepast, hierbij optimaal gebruik makend van de momenteel beschikbare medicamenten. Deze behandelwijze wordt ook wel treat-to-target (T2T) of tight control genoemd. De mate van ziekteactiviteit kan worden gemeten met de Disease Activity Score in 28 gewrichten (DAS28). Deze score wordt berekend met behulp van het aantal pijnlijke en gezwollen gewrichten, de bloedbezinking en de mate van algeheel welbevinden van de patiënt. Volgens onze werkdefinitie wordt remissie gedefinieerd als zijnde een DAS28 kleiner dan 2.6. Er bestaan echter ook andere definities van remissie, een eenduidige definitie ontbreekt tot op dit moment.

Uit klinische trials is gebleken dat een T2T behandelstrategie effectief is in het verlagen van de ziekteactiviteit en uiteindelijk in het bereiken van remissie in de behandeling van recent gediagnosticeerde RA. T2T is echter nog niet geïmplementeerd. In de dagelijkse klinische praktijk wordt de ziekteactiviteit niet consistent gemeten met een valide meetinstrument en medicatie wordt vaak niet aangepast ondanks de aanwezigheid van actieve ziekte. Het is de vraag of de veelbelovende resultaten van klinische trials met betrekking tot T2T kunnen worden vertaald naar de dagelijkse klinische praktijk. Klinische trials en de dagelijkse praktijk verschillen in meerdere opzichten van elkaar. Er wordt verondersteld dat de werkzaamheid van therapeutische interventies zoals wordt waargenomen in klinische trials, niet vaak wordt bereikt in de dagelijkse klinische praktijk. Dit kan onder andere worden verklaard door de strenge inclusie criteria die worden gehanteerd bij klinische trials (bijvoorbeeld met betrekking tot leeftijd, ziekteactiviteit en comorbiditeiten), waardoor de generaliseerbaarheid van de resultaten naar de praktijk wordt beperkt.

In het kader van het Dutch Rheumatoid Arthritis Monitoring (DREAM) remissie inductie cohortonderzoek is een T2T behandelstrategie, waarbij werd gestreefd naar het bereiken van DAS28-remissie, geïmplementeerd in verschillende ziekenhuizen in Nederland. In dit onderzoek worden patiënten waarbij onlangs de diagnose RA is gesteld op vaste momenten onderzocht en behandeld volgens een vast behandelschema met van tevoren vastgestelde beslismomenten over het aanpassen van de medicatie gericht op het zo snel mogelijk bereiken van remissie in de dagelijkse klinische praktijk. Het doel van dit

proefschrift was het evalueren van de effecten van de implementatie van deze T2T behandelstrategie.

In **Hoofdstuk 2** werden de eerstejaars resultaten gepresenteerd van de implementatie van de T2T strategie waarbij werd gestreefd naar het bereiken van remissie (gedefinieerd als een DAS28 < 2.6). Na zes en twaalf maanden follow-up was het percentage patiënten dat in remissie was hoog (respectievelijk 47% en 58%) en remissie werd snel bereikt. De eerste radiologische uitkomsten lieten zien dat er weinig radiologische schade was opgetreden en bij de meerderheid van de patiënten werd geen klinisch relevante radiologische progressie waargenomen. Optimaal gebruik van methotrexaat (MTX) (monotherapie gevolgd door combinatietherapie met andere conventionele disease-modifying antirheumatic drugs (DMARDs) indien nodig) bleek succesvol te zijn in het bereiken van het behandeldoel. In het eerste jaar kreeg slechts 10% van de patiënten anti-tumour necrosis factor α (anti-TNF) therapie voorgeschreven. Deze studie heeft laten zien dat een T2T strategie in combinatie met geprotocolleerde medicatiestappen haalbaar en succesvol is in het bereiken van remissie bij patiënten met recent gediagnosticeerde RA in de dagelijkse klinische praktijk.

In **hoofdstuk 3** werd getracht de vraag te beantwoorden of een behandelstrategie waarbij wordt gestreefd naar tight control van de ziekteactiviteit (ook wel T2T) effectiever is om remissie te bereiken na een jaar bij patiënten met vroege RA dan de reguliere behandeling (‘usual care’). De behandelstrategieën van twee vroege RA inceptie cohorten uit twee verschillende regio’s met patiënten die voldeden aan de American College of Rheumatology (ACR) classificatie criteria voor RA (2) zijn met elkaar vergeleken. Patiënten in de tight control groep werden behandeld volgens een T2T strategie waarbij gestreefd werd naar het bereiken van remissie (DREAM remissie inductie cohort). Patiënten in de usual care groep werden behandeld zonder DAS28-gestuurde behandelstappen. Na een jaar hadden meer patiënten in de tight control groep remissie bereikt dan in de usual care groep, met remissie percentages van respectievelijk 55% versus 30%. Remissie werd ook sneller bereikt met T2T. Tevens leidde T2T tot een grotere daling in DAS28, een groter aantal patiënten met lage ziekteactiviteit en grotere verbeteringen in fysiek functioneren en in de waardering van de patiënten over hun pijn en algehele gezondheid. In beide groepen werd met name een step-up behandelstrategie toegepast en het aantal patiënten dat anti-TNF middelen kreeg voorgeschreven was vergelijkbaar. De grootste verschillen tussen de behandelstrategieën in de groepen waren dat in de tight control groep bijna alle patiënten startten met MTX, terwijl MTX pas later werd gestart in de usual care groep. Verder werd combinatietherapie vaker voorgeschreven in de tight control groep. De

resultaten van deze studie hebben laten zien dat een T2T strategie waarbij wordt gestreefd naar het bereiken van remissie leidt tot een groter aantal patiënten dat remissie bereikt en dit ook sneller bereikt dan bij de reguliere behandeling bij vroege RA.

In **hoofdstuk 4** werd onderzocht of de gunstige effecten van de T2T strategie, zoals in de voorgaande hoofdstukken is laten zien, behouden blijven op de langere termijn. In dit hoofdstuk presenteerden we de resultaten van T2T met betrekking tot het bereiken van (stabiele) remissie, radiologische progressie, fysiek functioneren en gezondheidsgerelateerde kwaliteit van leven na drie jaar follow-up. Na drie jaar was de meerderheid van de patiënten in remissie, namelijk 62% en stabiele remissie (gedefinieerd als zes maanden of langer) werd geobserveerd bij 71% van de patiënten. Bij de meerderheid van deze patiënten werd stabiele remissie bereikt met behulp van conventionele DMARDs. Ook werden gunstige resultaten gezien met betrekking tot ziekteactiviteit, fysiek functioneren en gezondheidsgerelateerde kwaliteit van leven, waarbij significante verbeteringen werden gezien tijdens de eerste zes maanden van follow-up, waarna de resultaten stabiel bleven. De geobserveerde radiologische schade en progressie waren zeer klein, zelfs na drie jaar follow-up. Deze studie heeft laten zien dat de initiële gunstige effecten van T2T behouden blijven op de langere termijn.

Het doel van **hoofdstuk 5** was om te evalueren in hoeverre de T2T aanbevelingen zijn opgevolgd. We onderzochten of de aanbevelingen resulteerden in het regulier meten van de ziekteactiviteit met behulp van de DAS28 en of de medicatie werd aangepast volgens het behandeladvies (dat wil zeggen het medicatieprotocol), en wat eventueel de redenen waren voor afwijken. De resultaten van deze studie hebben laten zien dat de DAS28 op bijna alle cohortbezoeken is bepaald en dat de behandeling in de meerderheid van de bezoeken overeen kwam met het behandeladvies (69%). In het geval van het niet overeenkomen met de aanbevelingen werd over het algemeen een valide argument voor afwijken gegeven. De voornaamste reden voor afwijken was het gebrek aan overeenstemming tussen de mate van ziekteactiviteit volgens de reumatoloog en de gemeten DAS28. Met een percentage van 69% lijkt de compliantie aan de T2T aanbevelingen optimaal. Het streven naar een percentage van 100% is niet realistisch aangezien de behandeling van patiënten onderhevig is aan bijwerkingen en comorbiditeiten. Deze studie heeft laten zien dat de implementatie van T2T zeer goed haalbaar is in de dagelijkse klinische praktijk.

In **hoofdstuk 6** werden de resultaten gepresenteerd van een kosteneffectiviteits- en kostenutiliteitsanalyse van een T2T behandelstrategie gericht op het bereiken van

remissie in vergelijking met reguliere zorg (usual care) in de behandeling van patiënten met recent gediagnosticeerde RA in de dagelijkse klinische praktijk. De follow-up in deze studie was beperkt tot een periode van drie jaar. Er kan worden aangenomen dat met T2T meer inspanningen en kosten gemoeid zijn in het beginstadium van de ziekte, om daarmee gezondheidswinst en kostenbesparingen op langere termijn te realiseren. Het was de vraag of deze gezondheidsvoordelen opwegen tegen de extra kosten die gemoeid zijn met T2T. Om dit te onderzoeken is dezelfde vergelijking van patiëntengroepen als in hoofdstuk 3 gebruikt. Deze studie laat zien dat T2T effectiever is dan usual care: hogere remissiepercentages en een grotere winst in quality adjusted life years (QALYs) werden geobserveerd. De incrementele kosteneffectiviteitsratio was € 3.591 per patiënt in remissie na twee jaar en T2T was dominant na drie jaar. De incrementele kostenutiliteitsratio was € 19.410 per QALY na twee jaar en T2T was dominant na drie jaar. Na twee jaar was T2T geassocieerd met hogere kosten maar ook met een substantieel hogere effectiviteit in vergelijking met usual care. Na drie jaar wordt T2T waarschijnlijk kostenbesparend. De factoren die de kostenverschillen tussen T2T en usual care bepaalden waren anti-TNF therapie en hospitalisatie. Deze studie heeft laten zien dat T2T kosteneffectief is en deze behandeling de voorkeur verdient boven usual care.

Recentelijk heeft de ACR/European League Against Rheumatism (EULAR) nieuwe definities betreffende remissie in RA gepubliceerd. In **hoofdstuk 7** werd het patient global assessment (PGA) remissie criterium van de Booleaanse definitie van remissie bediscussieerd. Volgens deze definitie is een patiënt in remissie wanneer de volgende metingen ≤ 1 zijn: aantal pijnlijke gewrichten, aantal gezwollen gewrichten, C-reactief proteïne (mg/dL) en PGA (patiënt algeheel welbevinden op een visueel analoge schaal van 0-10). In de dagelijkse praktijk komt het vaak voor dat de patiënt hoger scoort op PGA dan zou worden verwacht op basis van de ziekteactiviteit. Dit suggereert dat de PGA niet louter wordt beïnvloed door het klinische ziekteproces. Daarom is het discutabel of een PGA score ≤ 1 gebruikt zou moeten worden als een criterium bij het bepalen van remissie. In deze studie hebben we de relatie onderzocht tussen het PGA remissie criterium en de klinische bevindingen bij de patiënt. Hieruit bleek dat patiënten regelmatig niet voldeden aan het PGA criterium, ondanks een goede klinische status. Blijkbaar zijn er ook andere factoren die kunnen leiden tot een PGA score die niet voldoet aan het criterium van ≤ 1, in afwezigheid van evidente gewrichtsinflammatie. Deze studie heeft laten zien dat het PGA criterium van de ACR/EULAR definitie van remissie in RA beperkingen heeft bij gebruik in de dagelijkse praktijk.

In **hoofdstuk 8** werden de bevindingen van de voorgaande hoofdstukken samengevat en bediscussieerd en aanbevelingen voor vervolgonderzoek gegeven. Dit proefschrift heeft laten zien dat het implementeren van een T2T behandelstrategie zeer effectief is in het bereiken van remissie bij patiënten met recent gediagnosticeerde RA in de dagelijkse klinische praktijk. De meerderheid van de patiënten bereikte remissie en dit vond in het algemeen vroeg in het ziekteproces plaats. Op de lange termijn (drie jaar) werd weinig gewrichtsschade, een verbeterd fysiek functioneren en een verbeterde kwaliteit van leven waargenomen. T2T blijkt beter in staat om de ziekte tot rust te brengen dan usual care. Tevens is de behandeling kosteneffectief op de langere termijn.

Het is algemeen geaccepteerd dat de behandeling van RA gericht moet zijn op het zo snel mogelijk onderdrukken van de ziekteactiviteit. De hypothese bestaat dat er een "window of opportunity" is waarin het ontstekingsproces meer gevoelig is voor behandeling dan later in het ziekteproces en de mogelijkheid bestaat om de ontstekingen te onderdrukken voordat er schade optreedt. Daarom is het van groot belang dat de ziekte zo snel mogelijk wordt gediagnosticeerd. MTX wordt beschouwd als de hoeksteen van de behandeling van RA, als initiële monotherapie en in combinatietherapieën. Dit proefschrift heeft laten zien dat direct starten met een optimale dosis MTX leidt tot een goede respons bij de meerderheid van de patiënten. In het geval van een suboptimale respons werd een combinatie van MTX en sulfasalazine voorgeschreven. De meerderheid van de patiënten bereikte (stabiele) remissie met een intensieve behandeling met conventionele DMARDs (monotherapie of combinatietherapie). Het voorschrijven van biologicals was slechts bij een klein percentage van de patiënten noodzakelijk.

Hoewel een T2T aanpak effectief is gebleken in het onderdrukken van de ziekteactiviteit en het bereiken van remissie zijn de T2T principes nog niet geïmplementeerd in alle reumatologie praktijken. De succesvolle implementatie van T2T, zoals is beschreven in dit proefschrift, wijst erop dat T2T ook haalbaar en effectief is in de dagelijkse klinische praktijk. Observationele data uit registers en cohortonderzoeken, zoals het onderzoek dat is beschreven in dit proefschrift, kunnen belangrijke aanvullende informatie verschaffen ten opzichte van klinische trials. De kracht van deze data ligt in het feit dat zij een betere weergave zijn van de dagelijkse praktijk, met betrekking tot de meer heterogene patiëntenpopulatie en wijze van behandeling. Daardoor kunnen de resultaten van observationele studies eenvoudiger gegeneraliseerd worden naar de algemene RA populatie. Andere positieve factoren zijn dat deze studies vaak grotere aantallen patiënten omvatten en een langere follow-up periode hebben dan klinische trials.

Het is nu algemeen geaccepteerd dat remissie het therapeutische doel zou moeten zijn bij de behandeling van RA. Desondanks is er op dit moment nog geen eenduidige definitie van remissie beschikbaar. Ook de recent gepubliceerde Booleaanse

definitie van remissie door ACR en EULAR lijkt niet optimaal te zijn. In dit proefschrift is remissie gedefinieerd volgens de DAS28 criteria. Echter, bij het streven naar remissie kan in principe elk van de beschikbare definities worden toegepast: het lijkt erop dat streven naar een van tevoren vastgesteld doel belangrijker is dan de exacte definitie van remissie.

De uitvoerbaarheid van T2T in de dagelijkse praktijk is afhankelijk van verschillende praktische en logistieke factoren. Onder andere het bereiken van consensus over de te volgen strategie, kennis over het meetinstrument dat gebruikt wordt bij het bepalen van de ziekteactiviteit, het inzetten van reumaverpleegkundigen en een digitaal systeem voor de opslag van data zijn factoren die de implementatie van T2T kunnen faciliteren. Patiënten moeten goed geïnformeerd worden over de toepassingen en het profijt van T2T.

Vervolgonderzoek zou zich moeten richten op de werkzaamheid, veiligheid en uitvoering van T2T in patiënten met recent gediagnosticeerde RA op de langere termijn, na drie jaar follow-up. Daarnaast is vervolgonderzoek nodig om te bepalen wat de meest optimale behandelstrategie is, aangezien in het cohortonderzoek dat beschreven is in dit proefschrift slechts één behandelstrategie is geëvalueerd. Niet alle patiënten waren in staat om remissie te bereiken. Het is ook van belang om voor deze patiëntengroep een passende strategie te ontwikkelen.

Een aanpak als T2T zou breed omarmd moeten worden om zo de klinische uitkomsten voor patiënten met recent gediagnosticeerde RA te optimaliseren en om zo hun gezondheidsgerelateerde kwaliteit van leven te verbeteren. Gebleken is dat het bereiken van remissie een realistisch doel is in de dagelijkse klinische praktijk en het bereiken van remissie zou dan ook de missie bij de behandeling van RA moeten zijn.

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Marloes Vermeer
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Curriculum Vitae

Marloes Vermeer was born in Enschede on March 22, 1984. After graduating from secondary school (Antheneum) at the Bonhoeffer College in Enschede in 2002, she studied Biology and Medical Laboratory Research with a major in Research and Development at Saxion in Enschede. After receiving her diploma in 2005, she studied Biomedical Sciences with a major in Epidemiology and a minor in Occupational and Environmental Health at the Radboud University Nijmegen. After graduating in August 2008, she started her PhD project on the effects of the implementation of a Treat-to-Target strategy in early rheumatoid arthritis at the department of Psychology, Health & Technology of the faculty of Behavioral Sciences at the University of Twente and the department of Rheumatology and Clinical Immunology of the Medisch Spectrum Twente in Enschede. The results of her PhD project are described in this thesis.

Marloes Vermeer is geboren op 22 maart 1984 te Enschede. In 2002 heeft ze haar VWO diploma behaald aan het Bonhoeffer College te Enschede. Daarna heeft ze de studie Biologie en Medisch Laboratoriumonderzoek met als afstudeerrichting Research & Development gevolgd aan de Saxion Hogeschool te Enschede. Na het behalen van haar diploma in 2005 is ze Biomedische Wetenschappen gaan studeren aan de Radboud Universiteit Nijmegen, met als hoofdvak Epidemiologie en als bijvak Arbeid, Milieu en Gezondheid. Na haar afstuderen in 2008 is ze binnen de afdeling Psychologie, Gezondheid & Technologie van de faculteit Gedragswetenschappen van de Universiteit Twente en de afdeling Reumatologie en Klinische Immunologie van het Medisch Spectrum Twente te Enschede begonnen met een promotieonderzoek naar de effecten van de implementatie van een Treat-to-Target strategie bij de behandeling van patiënten met recent gediagnosticeerde reumatoïde artritis. De resultaten van haar promotieonderzoek zijn beschreven in dit proefschrift.