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Targeted treatment in early rheumatoid arthritis

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Targeted treatment in early rheumatoid arthritis
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Chapter 1  General introduction
Chapter 2  Recent advances in the management of rheumatoid arthritis
Chapter 3  The BeSt story: on strategy trials in rheumatoid arthritis
Chapter 4  The impact of four dynamic goal-steered treatment strategies on the 5-year outcomes of rheumatoid arthritis patients in the BeSt study
Chapter 5  A decrease in disease activity score level is associated with a decrease in health assessment questionnaire score, independent of follow-up duration
Chapter 6  Simplified versions of the original disease activity score: validation in the BeSt trial
Chapter 7  Association with joint damage and physical functioning of nine composite indices and the 2011 ACR/EULAR remission criteria in rheumatoid arthritis
Chapter 8  Discontinuation of infliximab and potential predictors of persistent low disease activity
Chapter 9  Discontinuing treatment in patients with rheumatoid arthritis in sustained clinical remission
Chapter 10  Clinical synovitis in a particular joint is associated with progression of erosions and joint space narrowing in that same joint, but not in patients initially treated with infliximab
Chapter 11  A comparison between the simplified erosion and narrowing score and the Sharp-van der Heijde score
Chapter 12  Blood pressure changes in patients with recent onset rheumatoid arthritis treated with four different treatment strategies
Chapter 13  Summary and general discussion
Chapter 14  Nederlandse samenvatting
Appendix  Role of the funding source
Acknowledgements
Curriculum vitae
List of publications
Dankwoord
CHAPTER 1

General Introduction
GENERAL INTRODUCTION

This thesis is based on data of the BeSt study (Dutch acronym for Behandel Strategieen; treatment strategies), a large randomised controlled trial comparing four different treatment strategies in patients with recent-onset rheumatoid arthritis. After a brief overview of the clinical picture and pathophysiology of rheumatoid arthritis, an overview of the available treatment options is given, followed by an introduction of the concepts of early treatment, tight control and combination therapy. These three concepts form the basis of the four treatment strategies of the BeSt study.

Rheumatoid arthritis

Clinical picture

Rheumatoid arthritis is a systemic inflammatory auto-immune disease characterised by the presence of poly-articular inflammation of synovial tissue in diarthrodial joints, resulting in pain, swelling and stiffness. The metacarpophalangeal (MCP) joints, proximal interphalangeal (PIP) joints of the hands, the wrists and the metatarsophalangeal (MTP) joints of the feet are most commonly affected. Less frequently, larger joints are involved in the disease process. The disease course is heterogeneous, varying from a mild pattern, to a severe course with significant functional limitations, severe joint destruction, loss of quality of life and even death if not treated properly. In the short-term functional limitations are mainly determined by the presence of active synovitis, whereas in the long-term joint damage contributes significantly to functional limitations.

Joint damage

Radiological damage progression assessed on plain x-rays is one of the main outcomes in rheumatoid arthritis (RA) treatment. The amount of joint damage is highly variable among patients with rheumatoid arthritis. Some patients have already damage at baseline and will show rapid destruction if not treated properly, whereas others do not have any damage. Joint damage progression assessed on plain radiographs is related to disease activity and functional status and is a measure for disease severity and treatment response, with the advantage of easy access and limited costs.

Several methods to quantify joint damage have been developed, of which the methods of Sharp and Larsen and its modifications are most often used. The Sharp-method, modified by Van der Heijde is well-validated and commonly used in clinical trials. In total, 12 and 12 joints of hands and feet are assessed for erosions respectively (range per joint 0-5 in hands, 0-10 in feet) and 30 and 12 joints of hands and feet for joint space narrowing respectively (range per joint 0-4). The maximum erosion score is 280 and the maximum score for joint space narrowing is 168 points, with a total score ranging from 0-448.

To assess the effectiveness of treatment, joint damage progression scores rather than absolute joint damage scores are used. Therefore sets of radiographs of hands and feet of a period of interest are scored together to calculate progression scores. Measurement error can be reduced by using the average scores from two different readers who independently read the radiographs. There is no consensus on whether radiographs should be scored in random or in known time sequence. The method should be taken into account when interpreting radiological outcomes because scoring with known time sequence might overestimate joint damage while scoring in random order might result in a more conservative scoring approach leading to a decrease in signal-to-noise ratio. Joint damage progression has a skewed distribution: a minority of patients shows marked progression, whereas the majority shows little or no progression. Therefore only showing means with standard deviations or medians with interquartile ranges, information might be missed. With cumulative probability plots joint damage progression in every individual patient can be shown by depicting a single dot per patient. The Smallest Detectable Change can be used as a cut-off for distinguishing measurement error form ‘real’ progression.

A structured regular assessment of joint damage progression is not a routine part of clinical care. Regular performance of x-rays is however recommended. More structured assessments would help identifying patients showing progression of joint damage which is not always accompanied by clear clinical synovitis. Treatment change may inhibit this process which would be missed with clinical assessments alone. Drawbacks for the introduction of structured damage assessments in daily practice with e.g. the Sharp-van der Heijde method are that the method is comprehensive, time-consuming and requires training. Furthermore, rheumatologists might not be aware of the gain of structured damage assessments. An alternative might be the simplified erosion and narrowing score (SENS), a simplified version of the Sharp-van der Heijde score in which the number of joints with erosions or joint space narrowing are simply counted, without taking into account the grading of damage per joint, making it more feasible for clinical practice. The total score ranges from 0-86, with a maximum score of 44 for erosions and 42 for joint space narrowing.

Functional ability

A second important outcome in rheumatoid arthritis research and treatment is functional capacity, which can be measured using the validated health assessment questionnaire (HAQ) developed in 1980. Later, Siegert, et al validated the Dutch version of the HAQ. The HAQ is a self-report questionnaire including 20 questions in 3 sections: dressing and grooming, arising, eating, walking, hygiene, reach, grip and activities. The patients are asked to indicate the difficulty of the activities with four possible answers: 0, without any difficulty; 1, with some difficulty; 2, with much difficulty and 3, unable to do. The use of aids or devices and help from another person is taken along. The total score ranges from 0 to 3 (0=best; 3=worst). A difference of 0.22 is described as a minimally clinical important difference.

Extra-articular features

Besides the articular features, extra-articular manifestations may be present, such as lung fibrosis, pleuritis, scleritis, periarteritis, lymphadenopathy, amyloidosis, peripheral neuropathy, vasculitis and splenomegaly. Furthermore, rheumatoid arthritis is associated
with a higher prevalence of cardiovascular morbidity and mortality than in the general population. Inflammation, a shared feature in the pathophysiology of rheumatoid arthritis and atherosclerosis, seems to be the major contributor to the increased cardiovascular risk in RA patients, and adequate suppression of disease activity is necessary to lower cardiovascular risk.

Epidemiology
Rheumatoid arthritis is a common disease with a prevalence of about 0.5% to 1% and a mean annual incidence in north European countries of approximately 0.029% (range 0.024%-0.036%). The disease is more prevalent in women than in men (ratio 3:1) and the onset of symptoms is most often between 40 and 60 years of age.

Pathophysiology
The exact pathogenic mechanism of RA is unknown. In summary, it is thought that a combination of genetic (e.g. presence of shared epitope) and environmental factors (e.g. smoking) results in T-cell activation by the presentation of an unknown antigen by an antigen-presenting-cell. In the presence of costimuli, the T-cells become activated, migrate to the synovium and triggers activation of macrophages, B-cells, fibroblasts and osteoclasts and the production of proinflammatory cytokines, such as TNF, IL-1 and IL-6 within the synovial tissue. Activated B-lymphocytes can present antigens to T-cells continuing the immune response. Furthermore, B-lymphocytes can differentiate into plasma cells, producing (auto) antibodies. The total immune cascade, probably initiated by T-cell activation, results in hyperplasia of the synovium (pannus), neovascularisation and the accumulation of inflammatory cells, subsequently leading to clinical synovitis and joint destruction.

Autoantibodies
The discovery of the presence of autoantibodies contributed to the concept of RA being an autoimmune disorder. Two classes of auto-antibodies, rheumatoid factor and anti-citrullinated protein antibodies (ACPA), are present in approximately two-thirds of RA patients. Rheumatoid factors are antibodies directed against the Fc region of immunoglobulin G, first described in 1939. Rheumatoid factor is not specific for RA and can be found in other inflammatory diseases and in healthy individuals as well. ACPA are antibodies against citrullinated proteins. Citrullination is a posttranslational modification of arginine into citrulline catalysed by the enzyme peptidyl arginine deaminase. The presence of ACPA, as detected with a commercially available anti-CCP test, is highly specific for RA and is predictive for a more severe disease course. ACPA positive patients seem to have a different genetic background than ACPA negative RA patients. Therefore, the hypothesis that ACPA positive and ACPA negative disease are two distinct disease entities has been proposed. There is increasing evidence that ACPA play a pathogenic role in rheumatoid arthritis, although the exact mechanism is unknown. Both anti-CCP and rheumatoid factor can be present years before onset of the disease.

Classification and diagnosis
The term ‘Rheumatoid Arthritis’ was first used in 1859, by the British Rheumatologist Alfred Baring Garrod. Since then, different classification criteria have been proposed to distinguish rheumatoid arthritis from other inflammatory disease entities and to encourage the use of a uniform definition in clinical trials. Until the mid-1980s, the 1958 criteria were used, in which patients could be classified as having ‘probable’ or ‘definite RA’. Until May 2010, the classification criteria formulated by the American College of Rheumatology (ACR) in 1987 for rheumatoid arthritis were used. They included the following 7 items: 1. morning stiffness for at least 1 hour, 2. swelling (soft tissue or fluid) in at least 3 joints, 3. swelling (soft tissue or fluid) in hands (MCPh,PIP) or wrists, 4. asymmetrical distribution, 5. subcutaneous nodules, 6. positive rheumatoid factor and 7. radiographic changes on hands/wrist radiographs (erosions or juxta-articular osteoporosis). Criteria 1, 2, 3 and 4 had to be present for at least 6 weeks. Patients were classified as having rheumatoid arthritis if at least 4 out of 7 criteria were met. The 1987 RA criteria have shown value as classification criteria, but were not developed for diagnostic purposes. In early disease the criteria have poor sensitivity to diagnose RA, in particular the earliest manifestations of the disease. Features that might be prevented with accurate treatment, such as radiographic changes and subcutaneous nodules, are included in the 1987 criteria. It has been recognised that early treatment with antirheumatic therapy (disease-modifying antirheumatic drugs, or DMARDs) results in better prevention of radiological joint damage and better maintenance of functional ability than delayed treatment. It is hypothesised that the development of rheumatoid arthritis progresses on a continuous timeline, starting in the general population where in individuals with a combination of genetic and environmental risk factors alterations in the immune response occur, leading to autoreactivity. Subclinical synovitis progresses to clinical undifferentiated arthritis, and finally rheumatoid arthritis that meets the classification criteria. In order to start treatment early the diagnosis has to be made earlier. To facilitate this, in 2010 new ACR/EULAR classification criteria for rheumatoid arthritis have been developed. The new criteria consist of a scoring system including early clinical, serological and radiological findings in patients with one or more inflamed joints to estimate the chance that these are manifestations of early rheumatoid arthritis.

Shift in traditional treatment paradigms
The past decades great improvements in the treatment of rheumatoid arthritis have been made. Until the 1980s RA treatment was based on a pyramid strategy with the adagium ‘do no harm’ and ‘go low, go slow’. Treatment started with drugs that were considered to be the least toxic, like aspirin and NSAIDs. The next step was treatment with DMARDs in monotherapy. Because of concerns on toxicity, combination therapy was saved for a minority of patients with a severe disease course. New insights, i.e. the benefit of early introduction of DMARDs, tight control and the early use of combination treatment including corticosteroids or biologicals have led to the abandonment of the classic pyramid approach. How to use the available drugs in the best timing and
order has been the question behind the BeSt study which is the basis of this thesis. The next section starts with a brief overview of the available antirheumatic drugs, followed by explaining the changes and new insights from the past decades on how and when antirheumatic treatment should be directed.

**Treatment options**

**Conventional DMARDs**

A wide variety of DMARDs are registered for the treatment of rheumatoid arthritis. Methotrexate is considered to be the first DMARD of choice in the treatment of rheumatoid arthritis due to its clinical and radiological efficacy. High retention rates and limited costs. Besides the efficacy as monotherapy, there is widespread experience of methotrexate in combination with other DMARDs and corticosteroids, and in combination therapy methotrexate is able to increase the efficacy of biologicals. The most common side effects are reversible liver toxicity and gastro-intestinal complaints, which can be reduced by dose reduction and/or or subcutaneous use, and by concomitant use of folic acid, recommended in a dose of at least 5 mg per week. Less common side effects are myelosuppression (particularly associated with overdosing), lung fibrosis and pneumonitis.

Sulfasalazine is a conjugate of mesalazine (5-aminosalicylic acid) and sulfapyridine, with clinical and radiological efficacy in RA as well as efficacy in inflammatory bowel diseases. Sulfasalazine can be prescribed as monotherapy, or in combination with other DMARDs, although the additional value remains controversial. Side effects may include gastrointestinal complaints and transient elevations of liver enzymes. Acute myelosuppression and hemolytic anemia are rare but serious side effects.

Leflunomide is a pyrimidine synthesis inhibitor that has comparable clinical and radiological efficacy as methotrexate and sulfasalazine. Leflunomide has been used as part of a combination therapy, but there may be toxicity concerns when it was combined with methotrexate. Common side effects are gastrointestinal complaints, hypertension, asymptomatric transaminase elevations, skin rash and myelotoxicity. Other, less commonly used DMARDs are the antimalarials hydroxychloroquine and chloroquine (favourable safety profile, but limited efficacy as monotherapy). Ciclosporin A (positive effect on clinical and radiological outcomes, unfavourable toxicity profile with renal toxicity and hypertension), tacrolimus (good efficacy, slow mode of action, probably more toxicity) and azathioprine (moderate clinical efficacy, radiological efficacy inconclusive, unfavourable toxicity profile).

**Corticosteroids**

In 1949, Hench, et al. described the beneficial effect of glucocorticoids on the symptoms of RA. Since then, several randomised trials showed the efficacy of low-dose glucocorticoids (<10 mg) on clinical outcomes and on inhibiting joint destruction, alone, and in addition to DMARD therapy. Temporary treatment with a high dose prednisolone early in the disease course has shown to induce rapid reduction of inflammation, reduction of clinical symptoms and prevention of radiological damage, the base of one of the four treatment strategies of the BeSt study.

Toxicity associated with glucocorticoids is a concern, although the risk profile in low-dose regimens is probably less harmful than what was expected earlier. With higher dosages, glucocorticoids toxicity may increase. Therefore, moderate to high dose prednisolone are preferably given only during a short course. In 2007, a EULAR taskforce published evidence-based recommendations for the use of glucocorticoids in RA.

**Biologicals**

With the increasing understanding of the immunological background of rheumatoid arthritis, several new therapies have been developed specifically targeting cytokines and cells of the immune system which are thought to play a role in the disease process of RA. These new treatments are referred to as ‘biologicals’.

**Anti-TNF**

With the introduction of tumour necrosis factor alpha (TNF-α) inhibitors rheumatoid arthritis treatment changed considerably. Patients who were refractory to conventional DMARDs improved substantially under anti-TNF treatment on both clinical and radiological outcomes, a revolutionary step forward. Five TNF blocking agents are currently licensed for the treatment of RA: infliximab (a chimeric mouse-human monoclonal antibody), etanercept (TNF-α type II receptor/IGG1 fusion protein), adalimumab (humanized monoclonal antibody against TNF-α), certolizumab (polyethylene glycol (PEG)-olated humanized Fab fragment of a TNF antibody) and golimumab (a fully human monoclonal antibody). The combination of methotrexate and a TNF inhibitor has shown to be superior in reducing clinical symptoms of arthritis and inhibiting joint damage progression compared to either drug alone, both in established and in early RA. There have been no direct comparisons the efficacy of the different anti-TNFs in a randomised controlled trial. Indirect comparisons of clinical trial data suggested a comparable clinical efficacy. Due to high costs of anti-TNF therapy in many countries, including the Netherlands, treatment with TNF inhibitors is only refunded by health insurance companies if patients have failed on two or more conventional DMARDs including methotrexate and therefore the use of TNF inhibitors as initial treatment is restricted.

An increased incidence of tuberculosis infections was seen in patients treated with anti-TNF, mainly due to reactivation of latent tuberculosis infections. Therefore, screening is recommended prior to anti-TNF treatment, including the assessment of medical history, clinical examination, a purified protein derivate (PPD) skin test and a chest x-ray. In case of a latent infection, pretreatment with tuberculostatica is advised. Controversies exist on whether anti-TNF increase the risk for serious infections. Data from randomised clinical trials and follow up studies suggest that upper respiratory tract infections are the most common infections. Opportunistic infections have
been reported. Also the question whether anti-TNF treatment is associated with an increased risk for malignancies is still subject of debate. Rheumatoid arthritis itself is associated with such a risk. So far, there is no convincing evidence that the overall risk for malignancies is higher among anti-TNF treated patients.\textsuperscript{102,103,104}

Some studies suggest an inhibiting effect of TNF inhibitors on joint damage progression, irrespective of the clinical response. This disconnect has been shown on patient level. It is unknown whether such a disconnect is present at the individual joint level.\textsuperscript{107}

Other biologicals

After the success of the introduction of anti-TNF in the treatment of RA several other biologicals have been developed. Biologicals currently registered for RA treatment, other than targeting TNF, are: anakinra (IL-1 receptor antagonist),\textsuperscript{108} rituximab (B-cell depleter, anti-CD20),\textsuperscript{109,110} abatacept (blocks CD80/CD86:CD28 costimulatory signal required for full T-cell activation),\textsuperscript{111,112} and tocilizumab (anti-IL6).\textsuperscript{113-116} A variety of other targets are currently under investigation: e.g. the inhibition of various kinases.\textsuperscript{117} Anti-TNF is currently the first-choice biological for RA, due to its efficacy and longer experience.\textsuperscript{118} Despite the remarkable response on anti-TNF treatment, approximately 1/3 of patients fail to respond on anti-TNF.\textsuperscript{119} Subsequently, a second anti-TNF or a biological with another target can be chosen. With the expanding armamentarium of biologicals the options grow exponentially, but there is insufficient evidence what would be the best choice of treatment if patients fail a first anti-TNF.

Treatment concepts

Combination therapy

Abundant evidence showed that combination therapy is more effective than monotherapy, especially combination therapy including corticosteroids or a biological\textsuperscript{113,114} with limited toxicity. Unfortunately, many of these studies have a static design which might overestimate the advantage that combination therapy would have in daily practice, in which a more dynamic treatment approach is used.

Early treatment and the ‘window-of-opportunity’

Numerous studies demonstrated the importance of early introduction of DMARDs in order to improve clinical outcome\textsuperscript{120,121} and prevent joint damage progression.\textsuperscript{122} It has been proposed that by early introduction not only the joint damage progression that would have happened during the delay could be prevented, but that in addition the slope of the progression curve could be decreased.\textsuperscript{123} These findings support the intriguing window-of-opportunity hypothesis, which was first formulated during the 1990s.\textsuperscript{124,125}

The idea is that there exists a critical period, early in the disease course, in which the disease is more responsive to treatment, and the disease course can be altered resulting in sustained profit. It remains unclear how long this opportunity exists and what the biological basis is.

Tight control

The concept of tight control was introduced in the Tight Control for Rheumatoid Arthritis (TICORA) trial by Grigor et al, a randomised clinical trial comparing an intensively treated group versus a routinely treated group. The intensive group had significantly more improvement in disease activity and function, more clinical remission and less radiographic progression.\textsuperscript{126} Comparable results were seen in the Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA) trial, in which a routine group was compared to an intensively treated group with treatment adjustments based on a computerised decision program.\textsuperscript{127}

Tight control involves frequent visits to the outpatient clinics with frequent measurements of disease activity, setting a goal e.g. low disease activity or remission and frequently adjust treatment until the goal is achieved.\textsuperscript{128} The benefit of tight control has led to the international adoption of goal-steered treatment (treat to target). The combination of both concepts results in frequent evaluations of disease activity with treatment adjustments as long as a predefined target of disease activity (ideally remission, possibly low disease activity) is not yet reached. Recommendations on whether or how to adjust treatment when the target of low disease activity or remission is achieved are lacking. Tapering high dosages or combination therapies under strict control of disease activity may be the next step, with the possible benefits of limiting adverse events and costs but the possible disadvantage of a flare of disease. Evidence from systematic randomised controlled trials on if and how treatment should be tapered and discontinued is scarce.\textsuperscript{129-135}

The BeSe study has incorporated tapering and discontinuation of medication in patients with persistent low disease activity and discontinuation of all DMARDs in patients with persistent clinical remission in the protocol. Recently, an international taskforce published 10 recommendations on targeted treatment in rheumatoid arthritis based on a systematic literature search and expert opinion.\textsuperscript{136}

Disease activity and clinical remission

Disease activity

The disease activity of rheumatoid arthritis cannot entirely be expressed in one clinical measure. Therefore, composite indices for disease activity have been developed. The Disease Activity Score, shortly DAS, is a statistically derived composite index, developed by van der Heijde, et al.\textsuperscript{137,138} based on the judgment of rheumatologists on treatment adjustments in clinical practice. The DAS consists of 4 variables: 1. a 44 swollen joint count (SJC44); 2. the Ritchie Articular Index for assessing tenderness in 53 joints (RAI)\textsuperscript{139}; 3. the erythrocyte sedimentation rate (ESR); and 4. patients assessment of general health, assessed on a 100 mm Visual Analogue Scale (VAS). With the following formula the DAS can be calculated:\textsuperscript{140}

$$
DAS = 0.5398 \sqrt{RAI} + 0.06465 \times (SJC44) + 0.330 \ln(ESR) + 0.00722 \times \text{VAS}.
$$

Cut-off values have been identified in accordance with patients’ and rheumatologists’ evaluations, representing high disease activity, moderate disease activity, low disease activity or clinical remission. In general, a DAS >2.4 is considered to represent too high
disease activity, whereas a DAS<1.6 is equivalent to clinical remission. The DAS gives a general impression of the activity of the disease, can be used as a practical instrument to guide treatment decisions and can be used to introduce tight-controlled treatment into daily practice. Evidence on whether the treatment target should be low disease activity or remission is limited. New composite indices have been developed, adapted and simplified versions of the original DAS, like the disease activity score in 28 joints (DAS28, ignoring the joints of the feet), the clinical disease activity index (CDAI) and the simplified disease activity index (SDAI). As with the original DAS, for all these composite indices cut-offs for remission, low disease activity, moderate disease activity and high disease activity have been published. There is no consensus on which disease activity measure should be preferred. All indices has shown to be related to functional ability and joint damage progression, two main outcomes in RA research and treatment. Comparing the association between the different disease activity measures, functionality and joint damage progression is difficult since they had not all been compared in one study.

Defining clinical remission
Remission can be seen as a state of disease in which both physician and patient agree that the disease is completely suppressed and evidence of active disease can no longer be detected. Remission has become a realistic treatment goal in rheumatoid arthritis. That sounds easy; however finding a proper definition for remission in RA is a challenge. There exists a wide variety of clinical remission definitions, based on single measures, cut-off values of composite indices and Boolean criteria. ACR remission criteria, remission based on the clinical disease activity index (CDAI) and simplified disease activity index (SDAI) are generally considered to be strict. Remission based on DAS, DAS28 and single measures classify a higher percentage of patients in remission. An international taskforce developed ACR/EULAR remission criteria, a challenging job, while no gold standard exists. The general feeling was that existing criteria allowed residual disease activity. According to these criteria with the ‘one’-rule, remission is defined as no more than one swollen and/or one tender joint, a CRP level lower than 1 mg/dl and a patient global assessment of disease activity lower or equal to one on a 0-10 cm visual analogue scale. A distinct set of criteria for the use in clinical practice (without CRP level) and research (including CRP level) has been proposed.

The BeSt study
The new insights of early intensive tight-controlled treatment and the use of combination therapy have all been incorporated in the BeSt study (Dutch Acronym for Behandel Strategieën; treatment strategies), a unique randomised trial that compares four dynamic treatment strategies instead of individual therapies, using antirheumatic drugs and combinations of drugs in various orders. Designed in the late 1990s, it is ambitious in aiming at low disease activity for all patients. The study was conducted by the Foundation for Applied Rheumatology Research, a cooperation between rheumatologists working in 20 hospitals in the southwestern part of the Netherlands. The main question addressed in the BeSt study was: how to treat RA? Is it necessary to start with combination therapy in all patients or should these intensive therapies be reserved for patients failing on DMARD monotherapy? Between 2000 and 2002, 508 patients with active, recent-onset RA according to the 1987 classification criteria were randomly assigned into four treatment strategies. Group 1, sequential monotherapy (n=126) and group 2 (step up combination therapy, n=121) started both with methotrexate monotherapy and in case of insufficient response treatment was switched to another DMARD in monotherapy (group 1) or DMARDs were added one by one (group 2). Treatment groups 3 and 4 started both with combination therapy, group 3 with initial combination of methotrexate, sulfasalazine and prednisone (n=133) and group 4 with initial combination of methotrexate and the TNF inhibitor infliximab (n=128). In the treatment groups 1, 2 and 3 patients could also receive the combination of methotrexate and infliximab after failing on at least 3 conventional DMARDs. For all four treatment groups a stepwise protocol was defined, aiming at a DAS of 2.4 or lower (i.e. low disease activity, figure 1, page 64). For this purpose, every three months the DAS was calculated by trained nurses, blinded for treatment allocation to prevent bias. If the DAS was >2.4, the next step of the treatment protocol was taken. If the DAS was ≤2.4 for at least 6 months medication was tapered to a maintenance dose. Due to higher remission percentages than expected beforehand, from the third year onwards the possibility to discontinue DMARDs was incorporated in the protocol. If patients had a DAS <1.6 (clinical remission) for at least 6 months on a maintenance dose, the last DMARD could be tapered to 0. When a DAS ≥1.6 was measured, the last DMARD was immediately restarted. The discontinuation of DMARDs in prolonged clinical remission has not been studied before in a randomised trial early in the disease course. Primary outcomes were 3-monthly assessed functional ability (HAQ) and joint damage progression assessed on annual x-rays of hands and feet. Secondary outcomes were remission percentages (defined as DAS <1.6) with and without DMARDs and quality of life. In the first year of the trial, the initial combination therapy groups showed an earlier clinical improvement than the initial monotherapy groups. From 1 year onwards the clinical outcomes in the four groups were comparable as a result of continuously aiming at low disease activity with treatment adjustments if necessary. The initial combination therapy showed significantly less joint damage progression than the initial monotherapy groups during 4 years of follow-up. Furthermore, after 4 years, 43% of patients were in clinical remission and 13% of patients had successfully discontinued their DMARDs while retaining remission, with a median duration of 11 months. The prolongation of three-monthly follow-up visits until 5 and eventually until 10 years of follow-up in the BeSt study provided a unique dataset from 508 tightly followed, intensively treated RA patients, of whom a wealth of information has been gathered. Important questions needing to be answered with longer follow-up duration are whether the initial clinical improvements including functional capacity, quality of life and high remission percentages in all treatment groups can be maintained with the
continuation of DAS-steered therapy, aiming at low disease activity. Is aiming for low disease activity strict enough? Can the amount of joint damage be limited over time, preserving the association between the presence of synovitis and functional limitations and providing a rationale for continuing treating to target on the long term? In addition, longer follow-up duration will elucidate how many patients can maintain drug-free remission over time, coming close to cure. Are the differences in joint damage progression rates between the initial monotherapy groups and combination therapy groups seen after 4 years based on differences in clinical response in the first year or did initial combination therapies induce durable lower progression rates fitting in the window of opportunity hypothesis? Is starting DMARDs after fulfilling the 1987 classification criteria for RA early enough? How has RA changed in manifestations and outcomes when modern drugs and concepts of treatment are applied?

Outline of the thesis

In chapter 2 an overview of clinical aspects and treatment of RA for generalists is given. Chapter 3 reviews strategy trials in the treatment of RA as an introduction to the BeSt study. In chapter 4 the clinical and radiological results of the four treatment strategies of the BeSt study are described after 5 years of DAS-guided, tight-controlled treatment. A detailed analysis of the longitudinal relationship between changes in disease activity and functional capacity in the BeSt study is performed in chapter 5. In chapter 6 three simplified versions of the original DAS with adjusted easier tender joint counts were validated. Chapter 7 describes the results of a comparison between 9 disease activity measures and their relationship to functional ability and joint damage, including the three versions of the original DAS that were validated in chapter 6. Furthermore, an extensive comparison of remission definitions based on disease activity measures and the 2011 ACR/EULAR remission is described in this chapter. Chapter 8 and 9 focus on the question what to do if a preset treatment goal is reached. Can medication be tapered safely in all patients? Chapter 8 describes the cessation of infliximab after achieving low disease activity, predictors of persistent low disease activity and the effect of the reintroduction of infliximab for those who lost low disease activity. Chapter 9 gives an overview of the patients who discontinued all DMARDs because of longstanding clinical remission (drug-free remission), predictors of persistent drug-free remission and describes the effect of reintroduction of medication for those who lost drug-free remission. The relationship between clinical signs of synovitis and progression of erosions and joint space narrowing at the joint level is described in chapter 10. The associations are separately assessed for the different treatment groups and for hands versus feet. Chapter 11 compares 2 scoring methods to assess joint damage on x-rays: the comprehensive well-validated Sharp-Van der Heijde score and the quicker and easier simplified erosion and narrowing score. Chapter 12 describes the relationship between the level of disease activity and blood pressure and compares blood pressure changes among the four treatment arms. Finally, in chapter 13 the results of the thesis are summarised and discussed.


Recent advances in the management of rheumatoid arthritis

A clinical review

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ABSTRACT

Until the 1990s patients with rheumatoid arthritis were initially treated with aspirin or other non-steroidal anti-inflammatory drugs; disease modifying anti-rheumatic drugs (DMARDs), such as methotrexate, were introduced only as the disease progressed. Combined treatment with more than one DMARD was reserved for patients with the most severe disease. The outcome for most patients was functional deterioration with progressive damage. However, innovations in drugs, better tools for monitoring treatment, and tight control strategies have improved the outlook for patients with rheumatoid arthritis. Remission with limited radiological damage and no functional deterioration is now a realistic treatment goal. Several randomised controlled trials have shown that treatment with DMARDs, corticosteroids, and biological agents early in the course of disease can retard progression of disease, reduce joint destruction, and improve functional ability and health related quality of life. This, along with the introduction of new tools to monitor response to treatment, has led to a new treatment approach and improved outcomes. We review evidence from randomised trials, systematic reviews, and recently published guidelines and outline the new approach to treatment, emphasising the importance of early diagnosis, referral, and treatment.

REVIEW

Sources and selection criteria
We used recently published recommendations on the treatment of rheumatoid arthritis. We also searched the Cochrane Database of Systematic Reviews (without time limits) and performed PubMed and Embase searches (October 2008 to July 2010) using the keywords “rheumatoid arthritis” and “disease modifying anti-rheumatic drugs” or “biologics” and the names and the synonyms of the most commonly used disease modifying anti-rheumatic drugs separately. We selected well conducted systematic reviews, meta-analyses, and large randomised controlled trials. When no such studies were available, we considered small randomised control trials, cohort studies, and observational studies.

What is rheumatoid arthritis and who gets it?
Rheumatoid arthritis is a systemic inflammatory autoimmune disease with localised and general manifestations. It is characterised by poliarticular inflammation of synovial tissue, which causes pain, swelling, and stiffness of the joints of the hands, wrists, and feet in particular. It also results in functional limitations and may progress to joint destruction and extra-articular disease (box 1). Observational studies have shown that mortality rates in patients with rheumatoid arthritis are higher than in the general population. Rheumatoid arthritis has an estimated prevalence of 0.5-1.1% and an incidence of 20-50 per 100 000 person years in northern Europe and North America. Lower prevalences (0.1-0.7%) have been reported in southern Europe, South America, Asia, and the Middle East, with very low prevalences in some parts of Africa. Prevalence is high in Native Americans. The disease is more prevalent in women than in men (3:1 to 2:1). Cohort studies suggest that prevalence rises with age and peaks at 65-74 years.

Box 1 Extra-articular manifestations of rheumatoid arthritis

Rheumatoid nodules
Osteoporosis
Vasculitis
Lung fibrosis
Pleuritis
Scleritis
Pericarditis
Lymphadenopathy
Peripheral neuropathy
Splenomegaly
Amyloidosis
How is rheumatoid arthritis diagnosed?

**History**

Patients have pain, stiffness, and limited joint movement. Presentation may be classic, with symmetrical polyarthritis of the small joints of the hands and feet, but monoarthritis or oligoarthritis, including large joints as first manifestation, is not uncommon. Observational studies suggest that patients who present with monoarthritis or oligoarthritis are as likely to develop progressive joint damage as those who present with polyarthritis. Patients often report general symptoms, such as morning stiffness (not only in affected joints, lasting more than an hour), fatigue, fever, sweats, and weight loss. In early disease, functional limitations are determined by the presence of active synovitis, but in the long term joint damage is also a contributory factor.

**Examination**

Synovitis can be clinically diagnosed by examination of the joints (box 2). Palpation shows swelling within the joint, sometimes with bulging and pain on pressure. Movement, particularly (over)extension or rotation, is limited, and force is reduced—for example, when making a fist. Because the small joints of the feet may be difficult to assess separately, inflammation may be easier to detect if the metatarsal joints are squeezed together. Heat and redness may be apparent, but absence of these signs does not preclude inflammation. In later stages of disease, rheumatic nodules or deformation might be seen, typically with ulnar deviation of the metacarpophalangeal joints. No single test or set of criteria is available to diagnose rheumatoid arthritis. Classification criteria have been developed for use in research populations only, although they are sometimes used in clinical practice. Until recently, the 1987 classification criteria of the American College of Rheumatology (ACR) were used (box 3). New classification criteria with a higher sensitivity in early disease were developed in 2010 (table).

### Box 2 Signs of inflammatory arthritis

- **Pain**
- **Swelling**
- **Loss of function of the affected joint (flexion or rotation, resistance to hyper-extension)**
- **Sometimes heat**
- **Occasionally redness**
- **Morning stiffness (not only in swollen joints)**
- **Squeeze test: put tangential pressure on the metatarsophalangeal and metacarpophalangeal joints; if tender, suspect synovitis**
- **General symptoms such as fatigue, fever, weight loss, and sweats**

### Box 3 1987 American College of Rheumatology classification criteria

At least 4 items should be present; items 1-4 should be of at least 6 weeks’ duration
1. **Morning stiffness for at least one hour**
2. **Synovitis in three or more joints**
3. **Synovitis in hands or wrists**
4. **Symmetrical distribution**
5. **Subcutaneous nodules**
6. **Positive rheumatoid factor**
7. **Radiographic changes on radiographs of hands or wrists**

**Investigations by general practitioner**

Patients with clinical signs and symptoms of arthritis should be referred to a rheumatologist as early as possible. More than a 12 week delay in referral is associated with a reduced chance of drug-free remission and increased risk for progressive joint damage. Radiographs and laboratory assessments are not necessary before referral and may delay treatment. Once the presence of arthritis is established, these tests may help identify monoarthritis or oligoarthritis in the early phases of disease.

**Investigations by a specialist**

Investigations in newly diagnosed patients include measurement of acute phase reactants (to calculate disease activity), a full blood count, and autoantibody tests. When an infectious cause or crystal induced (poly)arthritis is suspected, aspiration of synovial fluid or synovial biopsy may be helpful. Ultrasound may show synovitis in joints that are clinically difficult to assess and may help guide synovial fluid aspiration. Addi-
Several methods are available to quantify joint damage on radiographs of hands and feet. The modified Sharp method is well validated and often used in clinical trials. In total, 44 joints of hands and feet are assessed for erosions (part A; score range per joint 0-5 in hands, 0-10 in feet) and 42 joints of hands and feet for joint space narrowing (part B; range per joint 0-4). The maximum score is 448. An increase in total score of 5 in one year is considered to be rapid radiological progression and carries a poor prognosis.

Overview of swollen and tender joint counts as components of disease activity scores. Part (A) shows the joints assessed for swelling in the 44 swollen joint count (white and dark grey; assessed for the presence (score 1) or absence (0) of swelling). For the 28 swollen and tender joint counts only the joints depicted in dark grey are assessed for the presence or absence of swelling or tenderness. Part B shows the Ritchie articular index. For each joint, tenderness is graded from 0 to 3 (0=not tender, 1=pain on pressure, 2=winced, 3=winced and withdrew). With this index joints are grouped, and for each group (depicted in separate grey tints; maximal 5 joints per group) the highest score is used. The white joints count as separate joints.

Overview of joint damage on radiographs of hands and feet. The modified Sharp method is well validated and often used in clinical trials. In total, 44 joints of hands and feet are assessed for erosions (part A; score range per joint 0-5 in hands, 0-10 in feet) and 42 joints of hands and feet for joint space narrowing (part B; range per joint 0-4). The maximum score is 448. An increase in total score of 5 in one year is considered to be rapid radiological progression and carries a poor prognosis.
Current treatment strategies can achieve a mean Health Assessment Questionnaire score of 0.6, 43% clinical remission, and 13% drug-free remission.11 Recently, an international taskforce published 10 recommendations on targeted treatment, which were based on high level evidence and expert opinion.16 It recommended that clinicians base treatment on a shared decision between patient and rheumatologist; maximise long term health related quality of life through control of symptoms, prevention of structural damage, normalisation of function and social participation, particularly through “abrogation of inflammation”; and target treatment by measuring disease activity and adjusting treatment accordingly.

When should treatment start?
A meta-analysis of trials and observational studies published in 2006 showed that early introduction of DMARDs prevents joint damage.17 Patients with more aggressive disease seemed to benefit most. Recent data from a large observational cohort suggest that the crucial “window of opportunity,” when the immune response is more responsive to treatment and the disease course can be altered, may be as short as 12 weeks.4

What drugs are effective early in disease?

Conventional disease modifying anti-rheumatic drugs
Many synthetic DMARDs are available for the treatment of rheumatoid arthritis, but methotrexate is the first line treatment. A recent meta-analysis found that it improves clinical and radiological outcomes, has an acceptable long term toxicity profile, is acceptable to patients, with good adherence rates, and is cost effective.14,15 EULAR guidelines published in 2010 consider methotrexate to be safe and effective in combination with other DMARDs. Methotrexate also seems to increase the efficacy of biological agents when given concurrently. The most common side effects are gastrointestinal problems and reversible liver toxicity, which can be reduced by subcutaneous administration and dose reduction or concomitant use of folic acid, according to recent international consensus guidelines.9 Other synthetic DMARDs that may be useful are sulfasalazine, leflunomide, hydroxychloroquine, and, less often, injectable gold, ciclosporin, and azathioprine. As with methotrexate, all conventional DMARDs need regular monitoring for safety.20 A recent systematic review and meta-analysis found that leflunomide was as effective as methotrexate; that sulfasalazine and injectable gold reduced signs and symptoms of rheumatoid arthritis and structural damage; and that ciclosporin, minocycline, tacrolimus, and hydroxychloroquine showed some efficacy in reducing the number of swollen joints.18

Corticosteroids
A systematic review of randomised controlled trials found that low to moderate dose (7.5-15 mg/day) oral glucocorticoids reduce joint destruction and improve symptoms.19 Glucocorticoids reduce disease activity quickly, so are useful as “bridging drugs” when treatment begins. Adding glucocorticoids to DMARD monotherapy or combinations of synthetic DMARDs retards the clinical course of disease and inhibits radiographic progression, an effect that can last for years.21 Randomised controlled trials have shown that temporary treatment with prednisolone combined with methotrexate and sulfasalazine (and hydroxychloroquine) early in the disease induces more rapid reduction of inflammation and, as a result, earlier reduction of clinical symptoms and prevention of radiological damage than DMARD monotherapy.22,23 Intra-articular glucocorticosteroids in combination with methotrexate can reduce local symptoms and may also prevent progression of joint damage. The optimal dose of glucocorticoids in combination treatment is unknown.

Because long term use of glucocorticoids may increase risk of cardiovascular disease, the occurrence of mood disturbances, and osteoporosis, experts advise cautious use of these drugs, with tapering as soon as symptoms are controlled.24,25 In 2007 a EULAR taskforce published recommendations for the use of oral glucocorticoids in rheumatoid arthritis with a focus on toxicity.

Biological agents
Several drugs have been developed that target cytokines and cells of the immune sys-
Recent advances in the management of rheumatoid arthritis

Chapter 2

There is no convincing evidence that the overall risk for cancer is higher for patients who have received TNF-α inhibitors. If appropriate have greatly reduced this complication.

Several biologicals with other targets have been developed and are being investigated.26 Expert guidelines recommend TNF-α inhibitors as first choice of biological agent. If a patient does not respond to a first anti-TNF-α agent, then a second one—rituximab, abatacept, or tocilizumab—can be considered, preferably in combination with methotrexate.67 No evidence supports the use of one second line treatment over another.

### Risk of cardiovascular disease

Recommendations on managing the risk of cardiovascular disease in patients with rheumatoid arthritis, based on systematic literature reviews, have recently been published.72 Rheumatoid arthritis carries a higher than normal risk for cardiovascular disease, probably as a result of the increased prevalence of traditional risk factors and the inflammatory burden. Observational studies suggest that risk scores should be multiplied by 1.5 if two of the following criteria are met: presence of rheumatoid factor or anti-citrullinated protein antibodies, disease duration greater than 10 years, or presence of extra-articular manifestations. Ongoing cardiovascular risk assessment is recommended for all patients. To reduce risk, good control of disease activity is mandatory, as well as adequate management of cardiovascular risk according to local guidelines.

### An evidence-based approach to treatment

Early recognition of arthritis and rapid referral to a rheumatologist are essential. Begin treatment immediately after diagnosis and aim for clinical remission or low disease activity.65 Start treatment with a single DMARD, preferably methotrexate (although NICE recommends adding another DMARD), combined with short term glucocorticoids.65,66,69,70 If no response is seen, consider introducing a TNF-α blocker rather than switching to a combination of traditional DMARDs.65 Some guidelines recommend TNF-α blockers and methotrexate as initial treatment in high risk patients.65,66,70 Consider cautiously reducing and stopping treatment in patients in stable clinical remission, with prompt reintroduction if the disease recurs.65 Further improvements in diagnostics and targeted treatments are needed to halt the disease process. The new classification criteria will enable patients with earlier stage disease to enter clinical trials. Future developments may enable chronicity and deterioration to be avoided and provide a cure for rheumatoid arthritis.

### Summary points

- Rheumatoid arthritis is a common autoimmune disease that can lead to serious functional limitations, joint destruction, extra-articular disease, poor quality of life, and premature death
- Early recognition of arthritis and speedy referral to a rheumatologist is essential
- Treatment should start early and aggressively to prevent functional limitations and structural damage
- Innovations in treatment and monitoring have resulted in patients achieving early and sustained clinical and radiographic remission
- Methotrexate is the first line drug, but in high risk patients early combination of methotrexate with prednisone or a tumour necrosis factor inhibitor improves outcomes

### Box 5 Biologics

**TNF-α inhibitors**
- Adalimumab: humanised monoclonal antibody against TNF-α
- Certolizumab: Fab fragment of a humanised TNF-α inhibitor monoclonal antibody
- Etanercept: humanised soluble recombinant TNF-α type II receptor-IgG1 fusion protein
- Golimumab: human monoclonal antibody against TNF-α
- Infliximab: a chimeric mouse-human monoclonal antibody against TNF-α

**Others**
- Anakinra: human recombinant interleukin 1 receptor antagonist
- Abatacept: an immunoglobulin and extracellular CTLA4 domain fusion protein that selectively inhibits T cell co-stimulation
- Rituximab: chimeric monoclonal anti-CD20 antibody that depletes B cells
- Tocilizumab: humanised monoclonal anti-interleukin 6 receptor antibody

**Summary points**

- Rheumatoid arthritis is a common autoimmune disease that can lead to serious functional limitations, joint destruction, extra-articular disease, poor quality of life, and premature death
- Early recognition of arthritis and speedy referral to a rheumatologist is essential
- Treatment should start early and aggressively to prevent functional limitations and structural damage
- Innovations in treatment and monitoring have resulted in patients achieving early and sustained clinical and radiographic remission
- Methotrexate is the first line drug, but in high risk patients early combination of methotrexate with prednisone or a tumour necrosis factor inhibitor improves outcomes
**Tips for non-specialists**

- Refer all patients with suspected inflammatory arthritis to a rheumatologist as soon as possible.
- Rheumatoid arthritis can have a gradual onset but damage still starts early. Avoid a wait and see approach or time consuming radiographs and laboratory tests.
- Early treatment is essential for improving and maintaining functional ability and quality of life, and prevention of joint damage.
- Be aware of and treat risk factors for cardiovascular disease because rheumatoid arthritis carries an increased risk.
- Be aware of possible infectious episodes in patients treated with prednisone or biologics (or both), which may require earlier treatment.

**Ongoing research**

- Constructing prediction models including biomarkers to optimise early diagnosis of rheumatoid arthritis and individualised treatments.
- Identifying the optimal target for targeted treatment.
- Developing a uniform definition of remission as the ultimate treatment goal.
- Directly comparing the efficacy and safety of various biologicals. Comparing biologicals to combination treatment, including prednisone in patients who have not been treated with disease modifying anti-rheumatic drugs.
- Identifying mechanisms and processes that can be targeted with new drugs.
- Identifying treatments and strategies that cure rheumatoid arthritis.

**REFERENCES**

Chapter 2


Chapter 3

The BeSt story: on strategy trials in rheumatoid arthritis

N.B. Klarenbeek, C.F. Allaart, P.J.S.M. Kerstens, T.W.J. Huizinga, B.A.C. Dijkmans

ABSTRACT

Purpose of review To give an overview of recent strategy trials for the treatment of rheumatoid arthritis (RA).

Recent findings Strategy studies showed a clear benefit of dynamic result-driven treatment towards tight control of disease activity compared with ‘usual care’ in RA-patients. In addition, treatment given after short symptom duration gives better outcomes than later initiation of treatment. In many trials, combination therapies, especially combinations with prednisolone or biologicals, were superior to monotherapies. Moreover, combination therapies were more effective if given early in the disease as compared with a delayed introduction, giving support to the window-of-opportunity hypothesis. In the BeSt study, initial combination therapy could be successfully discontinued in half of the patients, emphasising that ‘initial’ would mean ‘temporary’. Less evidence is available about initial combination in comparison with combination therapy with a shorter delay. Larger tight-controlled, goal-steered, dynamic strategy trials comparing initial combination therapy with a short-delay combination therapy will help to translate the use of initial (temporary) combination therapy into normal daily practice.

Summary Treatment strategy trials have demonstrated that in the majority of patients with RA the following approach is the most beneficial: goal-steered, dynamic treatment towards tight control of disease activity, including early introduction of (an) effective disease-modifying antirheumatic drug(s) in combination with prednisone or anti-tumour necrosis factor, which includes tapering of the medication if remission or low disease activity is achieved.

INTRODUCTION

The treatment options for rheumatoid arthritis (RA) patients have increased substantially in the past few decades. New insights led to new treatment paradigms, including early introduction of treatment, the use of various combination therapies (including traditional disease-modifying antirheumatic drugs (DMARDs), biologicals, corticosteroids) and response-driven treatment, in which remission appears to be an attainable goal. There have been numerous trials with head-to-head comparisons of different (combinations of) drugs. However, extrapolation to clinical practice is usually difficult. Daily practice is much more dynamic than the regimens in comparative drug trials. Therefore, strategy trials have been published, in which the emphasis was not on the comparison of individual drugs but on the application of the available treatment options in a continuous, dynamic, ‘real life’ approach. In this review we discuss important lessons from those strategy trials, with a focus on new (follow-up) trials published during the last year.

Choosing optimal treatment

One of the important issues tackled in strategy trials is: what is the optimal way to use DMARDs in clinical practice? It is clear that RA-patients benefit from early introduction of DMARDs. With the rising number of drugs available for the treatment for RA, numerous treatment sequences and combinations are possible. Comparative drug studies showed that initial combination therapy, including DMARDs with prednisolone or anti-tumour necrosis factor (anti-TNF) (but not combination therapy with conventional DMARDs alone) gives earlier improvement and better outcomes than initial monotherapy in most patients. However, it is not clear whether this is also the case in a dynamic strategy, whether there is an optimal timing of combination therapy and how dynamic treatment should be directed.

Recent (follow-up) studies comparing combinations of conventional DMARDs

The Combination Anti-Rheumatic Drugs in Early RA (CARDERA) trial (table 1), a randomised controlled trial (RCT) comparing methotrexate (MTX) + placebo with MTX along with prednisolone, ciclosporin or both, showed a significant reduction in the development of new erosions by adding either ciclosporin or prednisolone to MTX monotherapy. The lowest number of new erosions was seen with the combination of the three drugs. During the second year of the Ciclosporin, Methotrexate, Steroid in RA (CIMESTRA) trial (table 2) which had originally compared initial MTX monotherapy with a combination of MTX and ciclosporin, adding hydroxychloroquine (HQC) to MTX monotherapy was compared to changing MTX and ciclosporin to MTX and HQC. In both groups, patients were seen every 4 weeks with the absence of swollen joints as treatment goal. Individual swollen joints were injected with betamethason. After 2 years of treatment, the initial combination group continued to do better in terms of American College of
### Table 1: Important new randomised controlled trials published between November 2007 and December 2008

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Disease duration</th>
<th>Follow-up</th>
<th>Treatment groups</th>
<th>Placebo</th>
<th>Tight control</th>
<th>Result-driven</th>
<th>Clinical</th>
<th>Radiological</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verspagen et al.</td>
<td>299</td>
<td>&gt; 1 year</td>
<td>2 years</td>
<td>Intensive vs conventional strategy; all MTX step-up</td>
<td>No</td>
<td>Yes, monthly</td>
<td>Yes, remission in intense group</td>
<td>% with progression similar, if progression present conventional arm failed level of progression</td>
<td>Progression initial comb vs conventional</td>
<td>Slightly TPE reported and AE related withdrawals in intensive group</td>
</tr>
<tr>
<td>Emery et al.</td>
<td>541</td>
<td>3-2 years</td>
<td>1 year</td>
<td>MX, MX + ETA</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>JHAQ, DAS, 20% vs baseline (combination vs MTX)</td>
<td>No major differences</td>
<td>Pred hypertension, bone mineral density decrease, CVA</td>
</tr>
<tr>
<td>Choy et al.</td>
<td>467</td>
<td>&lt; 2 years</td>
<td>2 years</td>
<td>MX vs MX + CSA (CSA after 3 months) vs MX + step-down pred vs triple therapy</td>
<td>No</td>
<td>Yes, No</td>
<td>No</td>
<td>HAQ, DAS, progression (combination vs MTX)</td>
<td>No major differences</td>
<td>Pred hypertension, bone mineral density decrease, mouth ulcers, headaches, transient creatinine elevations</td>
</tr>
<tr>
<td>Saunders et al.</td>
<td>96</td>
<td>Symptom duration &lt; 5 years</td>
<td>1 year</td>
<td>SSZ step-up, SSZ + MX + HCQ, placebo (placebo increases)</td>
<td>No</td>
<td>Yes, monthly</td>
<td>Yes, DAS80 &lt; 52</td>
<td>No differences in DAS, remission rates (MTX vs SSZ, HCQ)</td>
<td>No differences between the groups</td>
<td>Not reported</td>
</tr>
<tr>
<td>Van Tuijl et al.</td>
<td>29</td>
<td>3 months-40 weeks</td>
<td>1 year</td>
<td>SSZ + MX + HCQ vs high dose step-down pred</td>
<td>No</td>
<td>Yes, after 8 weeks</td>
<td>No</td>
<td>High ACR remission rates with no difference between groups</td>
<td>Not reported</td>
<td>4 treatment related adverse events</td>
</tr>
<tr>
<td>Van Vellenhoven et al.</td>
<td>487</td>
<td>Symptom duration &lt; 1 year</td>
<td>1 year</td>
<td>All MX, after 3 months</td>
<td>No</td>
<td>No</td>
<td>Yes, Only at 24 months</td>
<td>ACR50 vs TEUE, 20 good response</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Soubrir et al.</td>
<td>64</td>
<td>&lt; 6 months</td>
<td>1 year</td>
<td>MX step-up (ADA added if DAS &gt; 3.2) vs MX + ADA parallel</td>
<td>No</td>
<td>Yes, monthly</td>
<td>Yes, DAS80 &lt; 52</td>
<td>No differences in ACR response and progression</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Leirisalo-Repo et al.</td>
<td>100</td>
<td>Symptom duration &lt; 1 year</td>
<td>1 year</td>
<td>FINRACo vs FINRACo + 5 mg IFX (FINRACo-MTX + SSZ + HQC + pred)</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Remission no difference in sustained remission (IFX vs placebo)</td>
<td>No differences</td>
<td>Not reported</td>
</tr>
<tr>
<td>Van Eijk et al.</td>
<td>82</td>
<td>Symptom duration &lt; 2 years</td>
<td>1 year</td>
<td>Step-up aiming at remission vs conventional treatment</td>
<td>No</td>
<td>Yes, monthly</td>
<td>Yes, remission in intensive group</td>
<td>No differences in DAS, HAQ, remission rates</td>
<td>No differences</td>
<td>Not medication related adverse events in both groups</td>
</tr>
</tbody>
</table>

MTX, methotrexate; CSA, cyclosporin A; HCQ, hydroxychloroquine; SSZ, sulfasalazine; pred, prednisolone; ETA, etanercept; ADA, adalimumab; IFX, infliximab; HAQ, health assessment questionnaire; DAS, disease activity score in 28 joints; AUC, area under the curve; ACR, American College of Rheumatology (ILAR), European League Against Rheumatism; AEs, adverse events.

### Table 2: Interesting follow-up studies of randomised controlled trials published or presented between November 2007 and December 2008

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Disease duration</th>
<th>Follow-up</th>
<th>Treatment groups</th>
<th>Placebo</th>
<th>Tight control</th>
<th>Result-driven</th>
<th>Clinical</th>
<th>Radiological</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van der Kooi et al.</td>
<td>508</td>
<td>5-1 years</td>
<td>4 years</td>
<td>Sequential monotherapy vs combination therapy vs initial comb SSZ + MX + pred vs initial comb MX + IFX</td>
<td>No</td>
<td>Yes, three-monthly</td>
<td>Yes, DAS &lt; 4</td>
<td>Earlier improvement in DAS, HAQ, remission % (initial comb vs monotherapy), after 2 years no difference, drug-free remission 8-14%</td>
<td>Progression initial comb vs initial monotherapy</td>
<td>No major differences</td>
</tr>
<tr>
<td>Van der Heijde et al.</td>
<td>682</td>
<td>6-10 years</td>
<td>3 years</td>
<td>MX, ETA, MX + ETA</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>JHAQ, DAS response, remission % with combination vs monotherapy</td>
<td>Progression with ETA vs MX</td>
<td>No major differences</td>
</tr>
<tr>
<td>Hetland et al.</td>
<td>160</td>
<td>&lt; 6 months</td>
<td>2 years</td>
<td>MX, MX + CSA (after randomisation), baseline joint count, HCQ added after week 6, both arms step-up</td>
<td>Yes</td>
<td>Yes, monthly</td>
<td>Yes, ACR response, DMARD free remission</td>
<td>FACR0 and 50, no differences in remission % and HAQ (combination vs monotherapy)</td>
<td>Progression after 11 years in combination group</td>
<td>Combination of transient creatinine elevations, effect not unclear</td>
</tr>
<tr>
<td>Ranstelho et al.</td>
<td>315</td>
<td>Symptom duration &gt; 6 months</td>
<td>1 year</td>
<td>SSZ vs MX + SSZ + HQC, placebo (placebo increases)</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Remission</td>
<td>No differences in DAS, HAQ, remission rates</td>
<td>Progression after 11 years in combination group</td>
</tr>
<tr>
<td>Van Tuijl et al.</td>
<td>195</td>
<td>&lt; 2 years</td>
<td>11 years</td>
<td>Initial SSZ vs MX + SSZ + pred, after 56 weeks no treatment protocol</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Initial better clinical response, after 5 years slightly lower remission and DAS28 (combination vs monotherapy, non-responders in protocol)</td>
<td>Progression until 5 years in combination group no significant differences</td>
<td>Withdrawals in combination group</td>
</tr>
</tbody>
</table>

MTX, methotrexate; CSA, cyclosporin A; HCQ, hydroxychloroquine; SSZ, sulfasalazine; pred, prednisolone; ETA, etanercept; IFX, infliximab; HAQ, health assessment questionnaire; DAS, disease activity score in 28 joints; AUC, area under the curve; ACR, American College of Rheumatology.
Chapter 3 The BeSt story: on strategy trials in rheumatoid arthritis

48% of patients with recent-onset RA combination therapy (SSZ, MTX, HCQ and prednisolone) is superior to SSZ monotherapy with significantly higher remission rates, less radiological damage and comparable toxicity, while aiming at remission. After 11 years of dynamic, remission-steered treatment, the initial combination group still had less radiological progression compared to the initial monotherapy group (p=0.04). The Finnish Rheumatoid Arthritis Combination therapy (FIN-RACo) trial showed that in patients with recent-onset RA combination therapy (SSZ, MTX, HCQ and prednisolone) is superior to SSZ monotherapy with significantly higher remission rates, less radiological damage and comparable toxicity, while aiming at remission. After 11 years of dynamic, remission-steered treatment, the initial combination group still had less radiological progression compared to the initial monotherapy group (p=0.04).

Recent (strategy) trials confirmed the beneficial effect of early combination therapy with conventional DMARDs, including prednisolone, in comparison with monotherapy.

Recent (follow-up) trials comparing combinations with biologicals

With the use of biologicals, the treatment of RA has changed considerably. Several trials confirmed that combination therapy with any of the available anti-TNF inhibitors and MTX led to better clinical responses, functional improvement, quality of life and less radiological damage progression compared to treatment with MTX and anti-TNF therapy alone. In patients with established RA the 3-years results of the Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes (TEMPO) trial showed that patients treated with a combination of etanercept and MTX had significantly better DAS, higher remission rates and more improvement in HAQ scores compared with patients treated with either drug alone. Treatment with etanercept, alone or with MTX combined, led to less radiological damage progression than treatment with methotrexate monotherapy. In patients with recent-onset RA, the Combination Of Methotrexate and Etanercept Trial (COMET) showed a comparable beneficial effect of the combination of MTX and etanercept over treatment with MTX alone. Fifty percent of the patients treated with combination therapy achieved clinical remission compared to 28% of patients treated with methotrexate alone (p<0.0001). Eighty percent and 59%, respectively, achieved radiographic non-progression (p<0.0001).

In the dynamic NEO-RACo trial, the original FIN-RACo combination therapy (MTX + SSZ + HCQ + prednisolone) and 5 doses of infliximab in the first 6 months of treatment was compared with the same combination with placebo. The aim was to achieve ACR remission, and a dynamic, remission-steered strategy was used. Patients were randomized to either a step-down or a step-up approach. In the step-down approach, patients were started on MTX monotherapy, and if they achieved remission, MTX was tapered. In the step-up approach, patients were started on SSZ monotherapy, and if they did not achieve remission, MTX was added. The dynamic, remission-steered approach was continued throughout the trial.

The results showed a significant difference in remission rates between the two approaches. Patients in the step-down approach were more likely to achieve remission and to maintain remission compared to those in the step-up approach. These findings are in accordance with previous studies, which have shown that a dynamic, remission-steered approach is effective in achieving and maintaining remission in rheumatoid arthritis.

In conclusion, recent (strategy) trials confirmed the beneficial effect of early combination therapy with conventional DMARDs, including prednisolone, in comparison with monotherapy.
remission. The addition of infliximab resulted in significantly higher remission rates (70% versus 53%) and significantly less radiological joint damage progression after 2 years (-0.2 versus 1.4).

Following the introduction of anti-TNF, several biologicals with different immunological targets are developed. Abatacept and tocilizumab are approved as therapies for patients with rheumatoid arthritis, as was rituximab, previously used in the treatment of hematological malignancies. In most countries, reimbursement policies have made these drugs available only for patients who have failed on anti-TNF therapy. The newer biologicals were individually evaluated as add-on vs methotrexate (or sometimes other DMARDs) treatment. Only tocilizumab (anti-IL6) was compared as monotherapy against MTX monotherapy in a parallel design in MTX-naive patients and was more effective than MTX monotherapy in ACR 20, 50 and 70 responses and DAS28 remission. The effect on radiological progression remains to be determined. Other new candidate treatments need to be evaluated. No conclusions can be made about long-term safety of the new biologicals.

**Minimal delayed combination versus initial combination**

The progression of time without effective treatment impairs functioning of RA-patients, and therefore needs to be shortened. The results of the BeSt study show that a delay of 6 to 9 months in clinical improvement, because of unsuccessful sequential or add-on treatment with conventional DMARDs, results in significantly more joint damage progression compared with patients treated with initial combination therapy. This suggests that with delayed introduction of combination therapy the window of opportunity can be missed. Also, delayed infliximab could be less often discontinued than if employed as initial treatment.

Although on the group level, initial combination therapy leads to better outcomes than delayed therapy, a part of the RA population responds well to MTX monotherapy. Unfortunately, at this time it is not possible to predict who will respond to MTX alone. Therefore, an approach with a short period of MTX monotherapy, followed by immediate introduction of combination therapy in case of insufficient response might be appropriate. This approach was used in the SWEFOT trial in which 487 recent-onset RA patients started with MTX monotherapy. If the DAS28 was at least 3.2 after 3-4 months, patients were randomised to either adding SSZ and HCQ to MTX (n=130) or adding infliximab to MTX (n=128). Unfortunately, the final design does not allow us to compare this strategy to initial combination therapy. However, SWEFOT demonstrated that following failure on MTX monotherapy, patients who received infliximab added to MTX had significantly higher remission rates (42% versus 26%) and higher ACR70 and 70 responses (29% and 13%, 16% and 8%, respectively) after 1 year than patients who received the combination of conventional DMARDs.

The GUEPARD trial presents a parallel comparison between initial MTX monotherapy (32 patients) and initial combination therapy with MTX + adalimumab (33 patients). If after 3 months, DAS28 was more than 3.2, adalimumab was added to MTX monotherapy or increased in the combination arm, whereas medication would be tapered and stopped if the DAS28 was 3.2 or less. As expected, patients treated with initial MTX and adalimumab combination therapy showed an earlier improvement in disease activity than patients treated with initial MTX monotherapy, with 64% versus 25% of patients achieving a low disease activity at 12 weeks (p=0.001). Because of the dynamic treatment protocol, after 1 year, the proportion of patients with low disease activity was similar in both groups (65% versus 64%, p=0.98) and there were no differences in joint damage progression among the (small) groups. Interestingly, the total use of adalimumab did not differ between the groups. For a patient, a delay in clinical improvement of 3 months or more would be relevant, leading to the suggestion that initial anti-TNF therapy may be the best option.

In STRategies in Early Arthritis Management (STREAM), a study in relatively mild RA patients, remission-steered treatment with initial MTX monotherapy followed by addition of anti-TNF was compared to ‘conventional DMARD treatment’. In both groups, high remission rates, good clinical responses and less radiological damage were seen, without significant differences. This might be due to relatively low patient numbers, due to the patient profiles or both.

**How to decide when to change medication?**

With the introduction of superior (combinations of) drugs to suppress disease activity, the approach to treatment decisions has also changed. A rapid reduction in the number of inflamed joints and in erythrocyte sedimentation rate and C-reactive protein is now achievable. The Tight Control for Rheumatoid Arthritis (TICORA) trial showed that better disease control is possible with disease activity driven treatment than with observational therapy decisions, with significantly lower disease activity, higher proportions of patients with a good response, higher remission rates and less radiological damage compared to the conventional-treated patients. The Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA) trial confirmed that tight-controlled treatment with a clear treatment goal is better than ‘traditional’ treatment. In this trial, decisions in the intensive arm were made based on a computerised decision program. The intensive treatment group showed significantly higher remission rates than the conventional treatment group (50% versus 37%, p=0.03) together with a higher turnover from low-dose MTX monotherapy to high-dose and combination therapy. In contrast to the TICORA trial, there was no clear difference in radiological progression between the two groups after 2-year follow-up.

The BeSt study showed that, with continuous steering at low disease activity, a comparable disease state can be achieved in all four groups, independent of initial treatment. The time to achieve low disease activity is longer in the initial monotherapy groups compared to the initial combination groups. Therefore, fewer treatment adjustments are needed when treatment starts with initial combination therapy. Post-hoc comparative studies of the results of the BeSt study with the conventionally treated RA patients from two Dutch Early Arthritis Cohorts also showed a clinical benefit of DAS-steered treatment.

In retrospect, it seems obvious that, regardless of the medication used, adjusting the medication in order to achieve a certain goal will lead to patients achieving that goal.
Only the time of achievement may differ with the strategy. The next questions are: what goal should we aim at and how ‘tight’ should tight control be? As discussed, a number of trials implemented the concept of tight control in their protocol, but no large trials compared different treatment goals. Van Tuyl et al. did a small (pilot) trial comparing treatment steered at achieving a low disease activity (DAS28≤3.2) or at achieving a low C-terminal cross-linking of type II (CTX-II) level (marker for cartilage degradation, ≤150 nmol/mmol). Twenty-one patients were randomised and treated with the same medication, starting with a combination of SSZ, MTX, HCQ and a tapered high close of prednisolone. After 40 weeks, 19 of 21 patients were in remission (DAS28 ≤2.6). Because of the limited patient number, no conclusions could be drawn on the usefulness of CTX-II in treatment decisions. Following FIN-RACo and NEO-RACo trials, the Dutch Rheumatoid Arthritis Monitoring Registry (DREAM) remission induction cohort has shown that in daily practice, a tight-controlled, DAS28 less than 2.6-steered, initial MTX monotherapy-based treatment strategy results in a high percentage of patients progressing to combination therapy as well as a high percentage (51%) achieving remission after 1 year. These results show that clinical remission seems to be an attainable goal. In general it is reasonable to expect that, if treatment is aimed at a lower level of disease activity, less loss of functioning and less joint damage will be observed, and more treatment adjustments in more patients. The frequency of controls will depend mostly on local logistics.

Translation to clinical practice
The most important consequence to draw from the strategy trials described in this review is that result-driven treatment is better than what used to be routine, ‘observational’ care. Frequent visits to the outpatient clinic with treatment adjustments based on specific, validated tools are necessary to reach the predefined goal as soon as possible. And it seems reasonable to steer at achieving remission. Many trials have demonstrated that immediate suppression of disease activity leads to earlier clinical improvement and less joint damage progression, and that, on the group level, combination therapy is superior to treatment with DMARD monotherapy, without a clear negative effect on toxicity (table 1 and 2). The BeSt trial, integrating tight control with DAS-steered therapy decisions while comparing four different treatment strategies where various combinations of various drugs were introduced at various times in the treatment of patients with recent-onset RA, probably comes closest to mimicking modern daily practice in a clinical trial.

The implementation into daily practice is a slowly going process. Regrettably, the benefits of early aggressive treatment vs the risk of overtreatment prevent rapid implementation in individual patients. Ideally, treatment is tailored for each patient separately, based on clinical characteristics, laboratory markers or both. Unfortunately, the correct prediction whether a patient will respond well to a certain therapy turns out to be difficult. Ongoing research will contribute to the understanding of the pathogenesis of RA and improve prediction models by, ideally, identification of new biomarkers.

Until accurate prediction is possible, the risk of undertreatment (loss of function, joint damage progression) versus the risk of overtreatment (toxicity) needs to be considered. Other barriers for the implementation of early combination therapy involve cost issues and concerns about safety of the newest drugs. In addition, some combinations are found complex to administer. Given the evidence from various trials, it is reasonable to expect most patients to benefit most from initial treatment with a combination of drugs, including either prednisolone or a TNF-blocker. When the goal is achieved, the possibility of overtreatment should be anticipated by using a flexible protocol, which allows tapering and discontinuation of medication in a tight-controlled setting.

New research is needed to go further. The continuous search for biomarkers of disease stage and predictors of treatment response is essential to proceed to more individually tailored treatment in the future. Given their obvious potential, the newer biologicals need to be studied earlier in the disease course in comparison with established treatment strategies. Various treatment strategies should be compared, with no or with minimal treatment delay, looking at the induction of drug-free clinical and radiological remission, safety and total societal costs. It has to be confirmed that implementing the results of such studies into daily practice is possible and to the benefit of RA patients.

Conclusion
From various trials, including the BeSt study, the following aspects of RA treatment turn out to be beneficial:

1. early introduction of effective treatment with minimal delay in introduction of combination therapy including prednisolone or TNF blockers;
2. result-driven (for instance DAS ≤2.4 or remission) treatment;
3. tight controlled (based on measurement of disease activity) treatment

These three aspects should be and are being implemented in the treatment of recent-onset RA patients. New trials will help to fine tune the timing of the most effective drugs, which include the newer biologicals.
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CHAPTER 4

The impact of four dynamic, goal-steered treatment strategies on the 5-year outcomes of rheumatoid arthritis patients in the BeSt study


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**ABSTRACT**

**Objective:** To compare clinical and radiological outcomes of four dynamic treatment strategies in recent-onset rheumatoid arthritis (RA) after 5 years follow-up.

**Methods:** 508 patients with recent-onset RA were randomly assigned into four treatment strategies: sequential monotherapy; step-up combination therapy; initial combination with prednisone; initial combination with infliximab. Treatment adjustments were made based on 3-monthly disease activity score (DAS) measurements (if DAS >2.4 next treatment step; if DAS ≤2.4 during ≥6 months taper to maintenance dose; if DAS <1.6 during ≥6 months stop antirheumatic treatment). Primary and secondary outcomes were functional ability, joint damage progression, health-related quality of life and (drug-free) remission percentages.

**Results:** After 5 years, 48% of patients were in clinical remission (DAS <1.6) and 14% in drug-free remission, irrespective of initial treatment. After an earlier improvement in functional ability and quality of life with initial combination therapy, from 1 year onwards clinical outcomes were comparable across the groups and stable during 5 years. The initial combination groups showed less joint damage in year 1. In years 2-5 annual progression was comparable across the groups. After 5 years, initial combination therapy resulted in significantly less joint damage progression, reflecting the earlier clinical response.

**Conclusion:** Irrespective of initial treatment, an impressive improvement in clinical and radiological outcomes of rheumatoid arthritis patients can be achieved with dynamic treatment aiming at reducing disease activity, leading to 48% remission, 14% drug-free remission and sustained functional improvement. Starting with combination therapy resulted in earlier clinical improvement and less joint damage, without more toxicity.

**INTRODUCTION**

Great improvements in the treatment of rheumatoid arthritis (RA) have been made in the past few decades. The evidence for the benefit of the early use of (combinations of) disease-modifying antirheumatic drugs (DMARDs) and biological agents, together with the introduction of dynamic tightly controlled treatment aiming at a predefined goal, has led to a shift in traditional treatment paradigms. It is not known what clinical and radiological outcomes can be expected in the longer term in RA patients treated according to an early, intensive treatment approach.

The BeSt (Behandel-Strategieën, Dutch for treatment strategies) study incorporated these new insights into early, goal-steered treatment by comparing four dynamic treatment strategies rather than individual therapies, using antirheumatic drugs and combinations of drugs in various orders. Designed in the late 1990s, it was ambitious in aiming at low disease activity, and introducing protocolised tapering and discontinuation of all antirheumatic drugs when clinical remission is achieved. Furthermore, it provides a unique patient cohort because it is, as far as we know, the only RA trial in which patients are still monitored every 3 months after 5 years of follow-up and protocolised treatment adjustments continue to be made aiming at low disease activity.

Here we present the clinical and radiological outcomes of the BeSt study after 5 years of follow-up. The main objectives were (1) to assess functional status, quality of life and the amount of joint damage after 5 years intensive, disease activity score (DAS)-directed treatment; (2) to assess whether initial improvements in functional ability and quality of life can be sustained; (3) to compare clinical outcomes and annual joint damage progression scores between the four treatment strategies; (4) to assess the percentage of patients in remission and drug-free remission and assess joint damage progression in these patients.

**PATIENTS AND METHODS**

**Study design**

The BeSt study design has previously been published in detail. It is a randomised single-blind clinical trial to evaluate the efficacy and safety of four treatment strategies in recent-onset RA patients. Based on 3-monthly disease activity measurements, treatment adjustments were made aimed at achieving and maintaining a DAS (44 joints) of 2.4 or less. It is designed and conducted by the Foundation for Applied Rheumatology Research, a collaboration between rheumatologists in the western part of The Netherlands.

**Patients**

Between March 2000 and August 2002, 508 patients from 20 hospitals in The Netherlands with DMARD-naïve RA according to the 1987 American College of Rheumatology criteria, ages 18 years or older, disease duration of 2 years or less, with active disease with six or more of 66 swollen joints and 6 or more of 68 tender joints, and either an erythrocyte
sedimentation rate of 28 mm/h or greater or a global health score of 20 mm or greater on a 100-mm visual analogue scale (0, best; 100, worst) gave informed consent.

Interventions
Patients were randomly assigned into four treatment strategies. Group 1 (sequential monotherapy, n=126) and group 2 (step-up combination therapy, n=121) started both with methotrexate monotherapy, whereas group 3 (initial combination therapy with prednisone, n=133) and group 4 (initial combination therapy with methotrexate and the tumour necrosis factor alpha inhibitor infliximab, n=128) started with combination therapy. In all groups, treatment adjustments were made based on 3-monthly disease activity measures, aiming at a DAS of 2.4 or less (low disease activity). The DAS was calculated by a trained nurse, who remained blinded to the treatment. If the DAS was greater than 2.4, the next treatment step was taken according to the fixed stepwise treatment protocol for each group (figure 1). If the DAS was 2.4 or less (low disease activity) for 6 months or longer, medication was tapered to a maintenance dose. Details of the drug doses in the different treatment steps were reported previously. 10 Routine laboratory measurements were performed 3-monthly. For all strategy arms the protocol allowed discontinuation or reduction to the lowest tolerated dose of drugs that, in the opinion of the treating physician, caused side-effects. From the third year of treatment, patients who had tapered to low-dose monotherapy and had a DAS less than 1.6 for at least 6 months tapered and discontinued the last DMARD. If the DAS increased above 1.6, the last DMARD was immediately restarted, and could not be discontinued again.

Study endpoints and assessments
Primary outcomes
Primary outcomes were functional ability measured every 3 months with the Dutch version of the health assessment questionnaire16 (HAQ; 0, best; 3, worst) and joint damage progression on radiographs of hands and feet measured with the Sharp-van der Heijde method (SHS; range 0-448 points).17 Annual radiographs of hands and feet at baseline and years 1, 2, 3, 4 and 5 were scored in one session per patient by two independent readers, blinded to treatment allocation, patient identity and in random time sequence. The mean scores of the two readers were used in the analysis.

Secondary outcomes
Health-related quality of life was measured with the medical outcomes study 36,18 3-monthly in the first 2 years of treatment and annually from year 2 onwards. Based on a reference population, 19 two norm-based summary scales were derived: the physical component scale (PCS) and mental component scale (MCS). By definition, the mean PCS and MCS of the reference population are 50 (SD 10). Higher scores represent better health.

Remission and drug-free remission percentages were calculated, using DAS less than 1.6 as the remission criterion. 15 We calculated the SHS progression in patients in sustained drug-free remission (remission ≥1 year) in their first full year drug-free.

Adverse events
All adverse events (self-reported, or evident from laboratory tests or yearly general physical examination) were recorded. Serious adverse events were defined as conditions that are life threatening or leading to death, malignancies, conditions leading to (prolongation of) hospitalisation or conditions leading to significant or permanent disability.
Chapter 4 5-year results of the BeSt study

### Statistical analysis

The software program SPSS version 16.0 was used, using the intention-to-treat principle for all results, except for the analysis of the proportions of patients in remission and drug-free remission where complete data were used. Characteristics at t=5 years were compared between the groups using analysis of variance, chi-square and Kruskal-Wallis when appropriate. Baseline PCS and MCS scores were compared with the reference population with a two-sample t test.

The outcomes HAQ, SHS and quality of life (PCS, MCS) were longitudinally analysed using linear mixed models (LMM). For each outcome the covariance structure with the lowest Akaike value was used.

To test whether there were differences in HAQ between the groups during 5 years of follow-up, a LMM with the outcome HAQ (21xHAQ per patient) was performed, with treatment group, time and their interaction as determinants (covariance matrix ARMA11).

In the second LMM log-transformed SHS-scores (to approach normality) of all years were compared to investigate whether there were differences in joint damage progression between the treatment groups over time, with time, randomisation and the interaction time*randomisation as determinants, corrected for log SHS of baseline, baseline C-reactive protein, age, gender, anticyclic citrullinated peptide, rheumatoid factor and baseline body mass index (covariance matrix unstructured).

Finally, LMM was used to assess whether there were differences in quality of life between the patients in the four treatment groups during 5 years of follow-up, with PCS and MCS as outcomes and randomisation and time as covariates (covariance matrix unstructured). This was done by calculating and comparing areas under the curve (AUC) between the treatment strategies under the custom hypothesis subcommand of the LMM (TEST in SPSS).

In all analyses comparing treatment groups, each treatment group was assessed independently and compared with the other groups one by one, without combining the results of treatment groups.

### Table 1: Baseline demographic and disease characteristics

<table>
<thead>
<tr>
<th></th>
<th>Sequential monotherapy (group 1)</th>
<th>Step-up combination therapy (group 2)</th>
<th>Initial combination with prednisone (group 3)</th>
<th>Initial combination with infliximab (group 4)</th>
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</thead>
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<tr>
<td><strong>Age, years</strong></td>
<td>54 (13)</td>
<td>54 (13)</td>
<td>55 (14)</td>
<td>54 (14)</td>
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<tr>
<td><strong>Women, n (%)</strong></td>
<td>85 (68)</td>
<td>87 (72)</td>
<td>88 (66)</td>
<td>83 (65)</td>
</tr>
<tr>
<td><strong>Symptom duration, weeks (median, IQR)</strong></td>
<td>23 (14-54)</td>
<td>26 (14-56)</td>
<td>23 (15-53)</td>
<td>23 (13-46)</td>
</tr>
<tr>
<td><strong>IgM rheumatoid factor positive, n (%)</strong></td>
<td>84 (67)</td>
<td>77 (64)</td>
<td>86 (66)</td>
<td>82 (64)</td>
</tr>
<tr>
<td><strong>DAS</strong></td>
<td>4.5 (0.9)</td>
<td>4.5 (0.8)</td>
<td>4.4 (0.9)</td>
<td>4.3 (0.9)</td>
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<tr>
<td><strong>HAQ 0-3 scale</strong></td>
<td>1.4 (0.7)</td>
<td>1.4 (0.6)</td>
<td>1.4 (0.7)</td>
<td>1.4 (0.7)</td>
</tr>
</tbody>
</table>

Values are the mean (SD) unless indicated otherwise. DAS, disease activity score (44 joints); HAQ, health assessment questionnaire.
Chapter 4 5-year results of the BeSt study

4

Figure 4 Changes in HAQ, remission percentages, physical and mental component scale of the short form 36 and Sharp-van der Heijde score during 5 years of follow-up. HAQ, health assessment questionnaire; MCS, mental component scale; PCS, physical component scale; SHS, Sharp-van der Heijde Score.

Results are displayed as n (%).

### Results

Baseline characteristics between the four treatment groups were comparable (table 1). Patients had high disease activity (mean DAS 4.4) at baseline with compromised functional ability (HAQ 1.4). Erosions on radiographs of hands and/or feet were present in 72% of patients. During 5 years of follow-up, 72 patients (15%) withdrew from the study (figure 2), 15 (12%), 27 (22%), 20 (15%), and 12 (9%) in groups 1-4 (group 2 vs group 4 p=0.05, other comparisons ns).

Treatment

The percentage of patients who had achieved the goal of DAS of 2.4 or less was similar in all groups (p=0.94, total 82%). The proportions of patients in each treatment step at t=5 years are depicted in figure 3. The initial monotherapy groups needed more treatment adjustments before achieving a DAS of 2.4 or less than the initial combination therapies. After 5 years 25%, 21%, 45% and 65% of patients in groups 1-4 were still on the initial treatment. Fifty per cent of patients in group 4 had permanently discontinued the initial treatment with infliximab because of a continuous good response, and 46% of patients in group 3 had successfully tapered and stopped prednisone. In groups 1-3, 41%, 12% and 21% had started delayed infliximab because of insufficient response to previous drugs, and 21%, 5%, and 11% were still treated with infliximab at t=5 years, compared with 19% in group 4. In group 2, 26% had started prednisone because of insufficient response to step-up therapy with conventional DMARDs, and 6% were still treated with prednisone at t=5 years, compared with 14% in group 3 (median dose 5 mg in both groups).

Details on annual prednisone and infliximab use are given in table 2.

Functional ability

Patients in the initial combination therapy groups experienced an earlier improvement in functional ability than the initial monotherapy groups (figure 4A). At the end of the first year, the functional capacity had improved substantially to a comparable level in all four groups, and this improvement was sustained until 5 years of follow-up. At t=5 years there were no significant differences in functional capacity between the groups (mean HAQ 0.58). No major differences between limitations on the eight subscales of the HAQ were observed (data not shown). When taking into account all HAQ scores during 5 years of follow-up, patients in group 4 had better HAQ scores over time than patients

### Functional ability

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in groups 1, 2 and 3 independently, and patients in group 3 had better HAQ scores than patients in groups 1 and 2 independently (LMM, p<0.001 for group 3 vs groups 1 and 2, p=0.01 for group 3 vs group 4). The mean HAQ score during follow-up was 0.70, 0.70, 0.62 and 0.54 in groups 1-4, respectively.

Quality of life
Quality of life (PCS and MCS) was lower at the beginning of the study compared to the reference population (33 vs normal 50 for PCS (p<0.001) and 47 vs 50 normal for MCS (p<0.001), figure 4C and 4D). The PCS improved earlier in groups 3 and 4 than in groups 1 and 2. After 1 year the mean PCS was increased to a comparable level in all four groups (mean 45, SD 10) and sustained until 5 years of follow-up, without significant differences between the groups (mean PCS (AUC per month) 43.5, 43.3, 44.1, 45.0 for groups 1-4; PCS p=0.09 for 1 vs 4, p=0.08 for 2 vs 4, p>0.36 for other comparisons).

The mean MCS improved to 52 (SD 9), which is slightly better than the healthy reference population. After 5 years of follow-up, we observed no differences in mean MCS between the treatment groups (mean MCS (AUC per month) 51.8, 51.0, 50.9, 51.2 for groups 1-4).

Radiological damage
In total, 2595 sets of radiographs were available, 479 (94%) from baseline and 446 (88%), 436 (86%), 432 (85%), 421 (83%), 381 (75%) from years 1-5. The interobserver intraclass correlation coefficient of the two readers for 5-0 change scores was 0.98. After 5 years, there was significantly more radiological progression in groups 1 and 2 than in groups 3 and 4, with median (mean) SHS progression of 3.5 (14.0), 2.5 (11.0), 1.0 (7.6) and 1.0 (6.0) units for groups 1-4, respectively (groups 1-2 vs group 4 p<0.01; group 1 vs group 3 p<0.01; other comparisons: ns). There were no differences in radiological joint damage progression between groups 3 and 4. Annual SHS progression rates were the highest in year 1 (mean 3.4), with significantly more progression in groups 1 and 2 than in groups 3 and 4 (LMM p<0.05, figure 4E). In the following years, progression scores continued to increase (mean annual progression 1.5, 1.1, 1.5, 1.6 in years 2-5; LMM p<0.02 for each year compared with the preceding year) without differences between the four groups.

Remission and drug-free remission
After 5 years, 48% of patients were in clinical remission defined as DAS less than 1.6 equally distributed among the groups (figure 4B). Of those, 46%, 51%, 65% and 81% of patients in groups 1-4 had achieved that on the initial therapy. Patients in remission after 5 years had significantly less joint damage progression (mean 7.6 vs 10.7; median 1.0 vs 2.5, p<0.001) and significantly better functional ability (mean HAQ 0.34 vs 0.79, p<0.001) than patients not in remission but with DAS of 2.4 or less.

After 5 years in these patients was 15 (IQR 0-7.8). Of the patients in sustained drug-free remission (definition 21 year, radiographs available in 41/48), 78% showed no joint damage progression (defined as >0 SHS units) in the first year of drug-free remission.

Safety
During 5 years follow-up, 437 (86%) patients experienced at least one adverse event. In total, 251 serious adverse events occurred in 152 (30%) patients, equally distributed among the treatment groups and over time (table 3, figure 5). The majority of the adverse events was mild to moderate and did not lead to treatment adjustments. Eleven of the 120 patients treated with initial combination with infliximab in group 4, and three of 52, none of 15 and three of 28 patients in groups 1-3 treated with delayed infliximab had an infliximab infusion reaction. During 5 years of treatment, the number of serious infections, malignancies and deaths (12 patients, table 3) were comparable across the groups.

![Figure 5](link)

**Figure 5** Distribution of serious adverse events among the treatment steps and over time. Each dot represent one serious adverse event.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Adverse events and serious adverse events during 5 years follow-up</th>
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<tr>
<td></td>
<td>Sequential monotherapy</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>n=126</td>
<td>n=121</td>
</tr>
<tr>
<td>Any adverse event during 5 years</td>
<td>110 (87)</td>
</tr>
<tr>
<td>Infections</td>
<td>56 (46)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>56 (46)</td>
</tr>
<tr>
<td>Dermal/mucosal</td>
<td>34 (27)</td>
</tr>
<tr>
<td>Neurological</td>
<td>27 (21)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>20 (16)</td>
</tr>
<tr>
<td>Infusion reactions</td>
<td>3 (52)</td>
</tr>
<tr>
<td>Any SAE during 5 years</td>
<td>42 (33)</td>
</tr>
<tr>
<td>Serious infection (n)</td>
<td>13</td>
</tr>
<tr>
<td>Malignancies (n)</td>
<td>5</td>
</tr>
<tr>
<td>Death (n)</td>
<td>3</td>
</tr>
</tbody>
</table>

*Numbers indicate the number (percentage) of patients, unless specified otherwise. SAE, serious adverse event. Causes of death were the following: pneumonia, pneumonia/encephalitis, non-small cell lung carcinoma (group 1); cerebrovascular accident, bronchial carcinoma, myocardial infarction (group 2); ovarian carcinoma, cerebrovascular accident (group 3); disseminated tuberculosis, myocardial infarction, septic arthritis, cerebrovascular accident (group 4).
In group 4 one patient was treated for disseminated tuberculosis, despite 6 months previous treatment with isoniazide because of latent tuberculosis before the start of infliximab, according to then current guidelines and the study protocol. She subsequently died of other infectious complications (year 2). No other tuberculosis occurred in the trial.

**DISCUSSION**

The BeSt study shows that with dynamic treatment with currently available drugs, an impressive clinical and radiological gain can be made in the majority of patients presenting with severe RA, resulting in significant and sustained improvements in daily functioning and quality of life over time and adequate suppression of joint damage progression, irrespective of initial treatment. Contrary to expectations, by aiming at low disease activity, 48% of patients achieved early clinical remission, showing the least damage progression and the best functional ability of all. Up to 19% of patients even achieved drug-free remission, enjoying a functional ability that is similar to the general population, without having damage progression.

Patients treated with initial combination therapy showed a more rapid improvement in disease activity, daily functioning and quality of life than patients treated with initial monotherapy, as shown earlier. The earlier clinical response in the first 6-9 months of treatment was reflected in significantly less joint damage progression in the initial combination therapy groups compared to the initial monotherapy groups in year 1. After 5 years of follow-up, the initial differences in joint damage progression are still present, although the annual progression rates in year 2-5 were comparable between the groups. Starting with combination therapy or reserving it for later did not affect toxicity. The initial combination arms showed an earlier clinical response than the initial monotherapy groups, but medication costs are substantially higher in the beginning of the study in the combination arms, especially in the initial combination arm with infliximab. This raises questions upon the cost-effectiveness of the early start of biological study in the combination arms, especially in the initial combination arm with infliximab. An early clinical response has been suggested to be relevant for maintenance of paid work. In line with this, the cost-utility analysis of the BeSt study after 2 years showed that patients treated with initial combination therapy groups were able to keep more paid work than initial monotherapy groups, which might (partly) compensate higher medication costs in groups 3 and 4. We are currently working on the 5-year cost-utility analysis that will elucidate which strategy is most cost-effective in the long term.

The long-term follow-up of the COBRA and FIN-RACo trials suggested a difference in slope in the amount of joint damage after 1-2 years between the combination and the monotherapy arms, whereas we did not observe a difference in annual progression from year 1 until year 5 between initial monotherapy and initial combination therapy. Differences in study design and patient populations might have contributed to this discrepancy and harms direct comparison: continuous protocolary (BeSt) versus non-protocolary treatment after 1-2 years (COBRA, FIN-RACo), differences in frequencies of radiographs and scoring methods, different medication schemes and control groups (sulphasalazine in COBRA and FIN-RACo vs methotrexate in BeSt) and different targets (remission in FIN-RACo, DAS ≤2.4 in BeSt, no targeted treatment in COBRA).

Reported remission percentages vary widely (10-65%) in various studies with recent-onset RA patients, as a result of differences in remission definitions, patient characteristics and study designs. Given the patients’ disease severity and bad prognostic outlook at baseline, it is remarkable that after 5 years, 48% of patients were in clinical remission and 31% of those in drug-free remission. The study is underpowered to evaluate whether there are differences in (drug-free) remission rates between the four treatment groups. As the patients all satisfied the 1987 American College of Rheumatology classification criteria for RA, they already had well established disease. It is tempting to speculate on the impact of starting effective, dynamic, DAS-directed therapy even earlier in the disease course.

Our results underline the importance of early, targeted treatment in RA. Rheumatologists should be aware that both the immediate and later outlook of newly diagnosed patients depend on early reduction of disease activity and consequent treatment adjustments until this goal is achieved. Various tools have been developed to measure disease activity, but measuring alone is not enough. The gain from using these tools lies in setting a goal and adjusting therapy until it is achieved. There is insufficient evidence on what the target should be. Aiming at remission may possibly lead to even better treatment outcomes. The recommendations of an international taskforce on treating to target will hopefully encourage rheumatologists to adopt targeted treatment in their daily practice.

Rather than comparing one static treatment with another, the BeSt study has integrated dynamic treatment into the trial protocol, to mimic daily practice. Taking it one step further, it has introduced protocolised tapering and discontinuation of medication into the trial design. We would like to encourage other research groups also to use a dynamic approach in future randomized clinical trials.

In conclusion, with dynamic treatment with currently available drugs an impressive improvement in clinical and radiological outcomes of patients with recent-onset rheumatoid arthritis can be achieved, leading to 48% remission and up to 19% drug-free remission, irrespective of initial treatment. Starting with combination therapy resulted in earlier clinical improvement and less joint damage progression than starting with monotherapy, without more toxicity. With treatment adjustments aiming at low disease activity, in all four strategy groups the initial clinical improvement is maintained until 5 years follow-up without deterioration.
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A decrease in disease activity score (DAS) level is associated with a decrease in health assessment questionnaire (HAQ) score, independent of follow-up duration


*both authors contributed equally

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Introduction

The introduction of (combinations) of disease-modifying antirheumatic drugs (DMARDS), corticosteroids and biologicals early in the disease course has improved the clinical and radiological outcomes of rheumatoid arthritis (RA) patients considerably. Further improvement has been made by treating patients according to a predefined target and adjusting therapy until that goal is reached.

An frequently used tool for treating to target is the disease activity score (DAS) and its simplifications, originally developed to compare treatment outcomes in clinical trials. The DAS can be used as a tool to guide treatment decisions in individual patients. An frequently used tool for treating to target is the disease activity score (DAS) and its simplifications, originally developed to compare treatment outcomes in clinical trials. The DAS can be used as a tool to guide treatment decisions in individual patients.

Furthermore, it is known from previous research that the DAS is related to the functional capacity of RA patients. It remains unclear whether actively aiming at a decrease in DAS will, independent of follow-up duration and even if the DAS level is already low, results in improvement in functional ability. Therefore, the objective of this analysis was to assess the association between a change in DAS and functional ability (as measured with the health assessment questionnaire (HAQ)) during 5 years of DAS-steered treatment in patients with recently diagnosed RA, while taking into account the absolute level of disease activity and follow-up duration.

Patients and Methods

We used 5-year follow-up data from a cohort of 508 patients with active RA, all fulfilling the American College for Rheumatology (ACR) classification criteria for RA and a disease duration ≤2 years, treated with the aim of achieving DAS ≤2.4. Treatment adjustments were made based on 3-monthly DAS calculations done by a research nurse blinded for treatment allocation. If the DAS was >2.4, the rheumatologist adjusted medication according to the previously described protocol per treatment arm. If the DAS was ≤2.4 for at least 6 consecutive months, medication was tapered until monotherapy at a low maintenance dose was achieved. Once this was done, and if DAS was <1.6 for at least 6 consecutive months, the last medication was tapered and stopped, but restarted again as soon as DAS was ≥1.6. Functional capacity was measured every 3 months using the Dutch version of the HAQ. A decrease in HAQ of at least 0.22 is considered to be a clinically meaningful improvement.

Statistical analysis

A linear mixed model (LMM), which combines multiple measurements per patient, uses all available data during follow-up, takes into account missing values and corrects for within-patient correlation, was used to assess the longitudinal relationship between DAS and HAQ. Twenty follow-up measurements of HAQ per patient, collected during 5 years follow-up, were used as outcome. The DAS 3 months earlier (previous DAS), the change in DAS in the preceding 3 months (delta DAS), and the time since baseline (log-transformed to approach linearity) were
added to the model as explanatory variables, as well as the two-way interactions previous DAS*delta DAS, delta DAS*ln time and previous DAS*ln time and the three-way interaction previous DAS*delta DAS*ln time. The previous HAQ (3 months earlier) was added to the model (first order autoregression) to model change in HAQ rather than absolute HAQ scores. This allows a longitudinal interpretation of the data (i.e., a change in DAS is associated with a change in HAQ) rather than a cross-sectional interpretation (patients with a high DAS have on average high HAQ). The following potential confounders were added one by one: treatment strategy, baseline body mass index (BMI), age, sex, symptom duration, anti-citrullinated peptide antibody (ACPA) status, rheumatoid factor (RF) status, baseline C-reactive protein (CRP) and Sharp-van der Heijde Score (SHS) at baseline and in the following years. As well as the variables described above added as fixed effects, two random effects were added (random slope with ln time and a random intercept) to correct for between-patients variance. The covariance structure with the lowest Akaike value was used (unstructured), that is, the covariance structure that fitted the model best, while taking into account the number of estimated parameters. SPSS version 16.0 (SPSS Inc., Chicago, Illinois, USA) was used for the analyses.

RESULTS

In the first LMM with all covariates and interactions, the three-way interaction previous DAS*delta DAS*ln time was not significantly associated with HAQ (p=0.25) and hence omitted from the analysis. In the next analysis the covariates and two-way interactions were added one by one. The previous DAS, delta DAS, ln time, and the previous HAQ significantly predicted HAQ (table 1). Furthermore, the two-way interaction previous DAS*delta DAS was significantly associated with HAQ, indicating that the association with delta DAS depends on the absolute level of DAS and that there was a non-linear relationship between DAS and HAQ. The two-way interaction delta DAS*ln time showed no significant association, indicating that the relationship of delta DAS with HAQ was not dependent on the progression of time since the start of treatment. Treatment strategy, sex, baseline BMI, age, symptom duration, ACPA, RF, CRP and SHS and SHS in the following years did not change the parameters. SPSS version 16.0 (SPSS Inc., Chicago, Illinois, USA) was used for the analyses.

![Table 1: Linear mixed model (LMM) results of predictors of outcome HAQ during 5 years of DAS-steered treatment.](image)

**TABLE 1** Linear mixed model (LMM) results of predictors of outcome HAQ during 5 years of DAS-steered treatment.

<table>
<thead>
<tr>
<th>Variable</th>
<th>β</th>
<th>95% CI</th>
<th>Explained variance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ln (time)</td>
<td>0.044</td>
<td>0.031–0.057</td>
<td>20</td>
</tr>
<tr>
<td>Previous HAQ</td>
<td>0.234</td>
<td>0.219–0.255</td>
<td>20</td>
</tr>
<tr>
<td>Previous DAS</td>
<td>0.213</td>
<td>0.200–0.226</td>
<td>28</td>
</tr>
<tr>
<td>Delta DAS (current DAS – previous DAS)</td>
<td>0.183</td>
<td>0.166–0.200</td>
<td>37</td>
</tr>
<tr>
<td>Previous DAS*delta DAS</td>
<td>0.022</td>
<td>0.016–0.027</td>
<td>37</td>
</tr>
</tbody>
</table>

DAS, disease activity score; HAQ, health assessment questionnaire; ln (time), natural logarithm of time since baseline; LMM, linear mixed model.

The intercept is 0.037 with a p-value of 0.15. It represents results of final multivariable LMM. In the right-hand column the increasing explained variance of the model is given (compared to a LMM with only a random intercept), by adding first a random slope with ln time (explained variance 18%), and then one by one variables as shown in the table.

* p<0.05.

The matrix illustrates the positive association between delta DAS and HAQ, indicating that with a larger decrease in DAS, the outcome HAQ will be lower. This positive relationship did not change significantly during 5 years follow-up. The model also shows that a decrease in DAS resulting in a still high DAS has less impact on improving

![Figure 1: Matrix representation of predicted health assessment questionnaire (HAQ) score improvement after 3 months (A) and after 5 years of follow-up (B) based on HAQ and disease activity score (DAS) 3 months earlier, and change in DAS in the 3 preceding months. Clinically relevant HAQ decrease of ≥ 0.22 are shown in dark grey, smaller decreases in white, combinations that are unlikely to occur in real life (HAQ-DAS discrepancies) in lighter grey.](image)

**FIGURE 1** Matrix representation of predicted health assessment questionnaire (HAQ) score improvement after 3 months (A) and after 5 years of follow-up (B) based on HAQ and disease activity score (DAS) 3 months earlier, and change in DAS in the 3 preceding months. Clinically relevant HAQ decrease of ≥ 0.22 are shown in dark grey, smaller decreases in white, combinations that are unlikely to occur in real life (HAQ-DAS discrepancies) in lighter grey.
HAQ than a similar decrease resulting in a low DAS, given a similar previous HAQ. To illustrate, at DAS 4.5 and HAQ 1.5, a subsequent DAS improvement at 3 months of 1.0 was associated with a HAQ improvement of 0.5, whereas at DAS 2.4 and HAQ 1.5 the estimated HAQ improvement was 0.9.

DISCUSSION

This study shows that during 5 years of DAS-steered treatment in patients with recent-onset RA, a decrease in DAS is associated with a decrease in HAQ. The magnitude of HAQ improvement depends on the size of DAS decrease and on the absolute DAS level, but the DAS-HAQ association is independent of follow-up duration during 5 years. There appears to be no ‘lowest optimum’ for the DAS, since further lowering the residual disease activity, is likely to further decrease the HAQ and potentially improve the patient’s functional ability, unless there is little to gain.

The matrix based on the prediction formula derived from the linear mixed model illustrates the relationship between DAS, previous DAS, delta DAS, time and HAQ, and its interactions. It shows how a change in DAS results in a change in HAQ, taking into account time since baseline and absolute DAS level. By showing the relationship between DAS and HAQ in a DAS-steered treated cohort, our results expand on several previous studies in non-DAS steered cohorts.11 Welsing, et al.12 showed that the positive relationship between DAS and HAQ could no longer be demonstrated by the BeSt study inclusion criteria14, the patients included in this analysis of follow-up, in contrast to earlier studies in which the HAQ worsened after 3-6 years.10,12 Although various studies illustrate that DAS-steered treatment results in better outcomes of aiming at lower disease activity, including in patients with milder disease. Although various studies illustrate that DAS-steered treatment results in better outcomes than non-DAS-steered treatment, it appears that in daily practice old routines are difficult to change. Van Hulst, et al. found that rheumatologists adjusted medication only in one of three visits where disease activity was above target (67% of visits).19 Our results argue against reluctance in treatment adjustments and clearly emphasise the importance to actively aiming to decreasing DAS.

In conclusion, our results may encourage physicians to adjust treatment to aim at a lower DAS in order to achieve better functional ability for their patients.

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CHAPTER 6

Simplified versions of the original disease activity score

Validation in the BeSt trial

R. Koevoets, N.B. Klarenbeek, M Güler-Yüksel, M. van Oosterhout, M.V. van Krugten, PJ.S.M. Kerstens, TWJ. Huizinga, B.A.C. Dijkmans, D.M.F.M. van der Heijde, C.F. Allaart

Ann Rheum Dis 2011; 70: 1471-1474
Chapter 6

Simplified versions of the original DAS

ABSTRACT

Objective: To evaluate three disease activity score (DAS) alternatives without the Ritchie articular index (RAI). To compare the use of patient’s global assessment of disease activity (PGA) versus global assessment of health (GH) in DAS, DAS alternatives and DAS28.

Methods: Data from the BeSt study were used, a treatment strategy trial in early rheumatoid arthritis patients aiming at a DAS ≤2.4. DAS alternatives were DAS 0–1, with the RAI (0–3) reduced to a no–yes (0–1) score, DAS tender joint count 53 (DAS TJC53), with a 0–1 TJC in 53 separate joints and DAS TJC44 in 44 joints. Correlation patterns, mean difference from original DAS, classification differences in disease activity level and patient percentages with radiological damage progression per level were determined for all scores.

Results: In the majority of patients the scores were equal and correlation was high. Mean differences with the DAS at year 1 were −0.03 for DAS 0–1, 0.18 for DAS TJC53 and 0.11 for DAS TJC44. Classification agreement between scores was high (k year 1 0.76–0.98). Patient percentages with joint damage progression were similar for all scores. DAS, DAS alternative and DAS28 perform similarly using either PGA or GH.

Conclusion: DAS variants without the RAI perform comparably to the original DAS and may be chosen as alternatives. PGA can replace GH in the DAS, the alternatives and DAS28.

INTRODUCTION

Measuring disease outcome in rheumatoid arthritis (RA) is important to evaluate response to treatment. Recent recommendations for the management of RA propose measurement by validated composite scores including joint counts.1,2 The disease activity score (DAS) was the first composite measure developed to assess and compare disease activity in patients and patient groups. The DAS includes a swollen joint count in 44 joints, the Ritchie articular index (RAI)3 for evaluation of joint tenderness in 53 joints, erythrocyte sedimentation rate (ESR) and a visual analogue scale (VAS) for patients’ global assessment of disease activity (PGA) or of general health (GH).4 However, the DAS with VAS–PGA is not yet validated. The DAS28 was introduced as a simplification with a no–yes swollen and tender joint count (TJC) in 28 individual joints.5 Although in general the usefulness and importance of the DAS and DAS28 are well accepted,6 implementation in daily practice remains challenging. Some find that the DAS28 unjustly neglects the feet, but other scores might be too time consuming.7,8 The RAI may be subjective and complicated, as it is a 0–3 graded evaluation of the severity of tenderness and uses joint groups of which only the highest score per group counts. Alternatives to the DAS, including more than 28 joints without the RAI, might be more attractive to use in daily routine or clinical trials. This study aims to evaluate three variations of the DAS compared with the original DAS. In addition, we compared DAS, DAS variations and DAS28 using VAS–GH or VAS–PGA.

PATIENTS AND METHODS

Data from the BeSt trial were used, a randomised clinical trial with 3-monthly assessments aiming at a DAS of 2.4 or less by subsequent treatment adjustments.9 All follow-up visits included a full 68/66 graded joint count for tenderness and swelling, as well as measurements of VAS–GH, VAS–PGA and ESR. The current analysis was performed based on 467 patients with complete data at 1 year follow-up. The DAS and DAS28 were calculated using the following formulae: DAS = 0.5398√(RAI) + 0.06465(SJC44) + 0.330ln(ESR) + 0.00722(VAS) and DAS28 = 0.56√(TJC28) + 0.28√(SJC28) + 0.70ln(ESR) + 0.014(VAS).

DAS alternatives were derived as follows: the DAS 0–1 was calculated by the substitution of a RAI greater than 0 with ‘1’, while the RAI ‘0’ score remained ‘0’, resulting in a maximum TJC of 26. The DAS TJC53 was calculated with a ‘0’=no/‘1’=yes TJC in the 53 joints originally assessed within the RAI, but without grouping, resulting in a maximum TJC of 53. The DAS TJC44 was calculated with a TJC of ‘0’=no/‘1’=yes in the same 44 joints that are assessed for swelling in the DAS. All DAS variations, as well as the original DAS and DAS28, were calculated with VAS–PGA and VAS–GH.

Pearson’s correlation coefficients were calculated between the original DAS and DAS alternatives. The mean of these two measurements and the mean difference was calculated at year 1 and displayed in Bland–Altman plots with limits of agreement of 1.96*SD.
mean difference. Patients were categorised according to previously published cut-offs into remission, low disease activity (LDA), moderate disease activity (MDA) or high disease activity (HDA).\textsuperscript{10–14} Percentage agreement and $\kappa$ statistics were calculated to assess agreement between categorisation.

An area under the curve (AUC) DAS was calculated between 3 and 12 months for all scores separately using the formula: $(0.5 \times \text{DAS}_{\text{months}1} + \text{DAS}_{\text{months}2} + \text{DAS}_{\text{months}3} + 0.5 \times \text{DAS}_{\text{months}4})/3$. Baseline scores were excluded from the analysis to avoid skewness due to required HDA at inclusion.

The AUC DAS results, indicating disease activity over time, were categorised into remission, LDA, MDA and HDA. Next, the percentages of patients with a greater than 5 point Sharp van der Heijde score (SHS) progression between baseline and year 1 (consistent with the smallest detectable change and indicating rapid radiological progression) were compared in all categories for all disease activity scores. Finally, the ability of DAS alternatives to detect treatment differences at 3 months follow-up was assessed using the difference in scores between baseline and 3 months.

**RESULTS**

All patients had early (<2 years) RA and active disease at baseline with a mean (SD) DAS of 4.4 (0.9). At year 1 ($n=467$) median (range) RAI was $3.0$ (0–52), RAI 0–1 $3.0$ (0–23), TJ53 4.0 (0–50), TJC44 3.0 (0–44) and TJC28 2.0 (0–28).

Correlation was high for all DAS alternatives compared with the original DAS, and ranged between 0.96 and 0.99 ($p<0.01$) at baseline and between 0.97 and 1.00 ($p<0.01$) at year 1. Correlation between VAS–PGA and VAS–GH at five time points was limited ($r=0.5–0.8$, $p<0.01$). Nevertheless, for the original DAS, DAS alternatives and DAS28, all versions with VAS–GH correlated excellently to corresponding versions with VAS–PGA ($r=0.99–1.00$, $p<0.01$), both at baseline and year 1.

Figure 1 illustrates high agreement between DAS alternatives and the original DAS. DAS 0–1 shows a high accordance with the original DAS, whereas DAS TJ53 and DAS TJC44 are occasionally higher, as demonstrated by the higher mean difference and broader agreement limits. However, most scores remain unchanged compared with the original DAS. DAS, DAS alternatives and DAS28 perform similarly using either VAS–PGA or VAS–GH. Categorisation of all patients by different DAS is presented in table 1. The percentage of overall agreement for all separate DAS at year 1 was high (range 82.9–98.5%), chance corrected agreement as calculated by Cohen’s $\kappa$ ranged from 0.76 to 0.98. Significant disagreement between categorisation, for example LDA versus HDA or remission versus HDA was very rare (table 1). Chance corrected agreement for all scores with VAS–GH versus VAS–PGA ranged from 0.85 to 0.94. Both correlation and (chance corrected) agreement between the original DAS and alternatives using either VAS score did not change over time (data not shown).

The percentages of patients with rapid radiological progression (RRP; >5 points SHS in year 1) are represented in table 2. All DAS alternatives show comparable percentages of patients with RRP within categories of disease activity level using either VAS. Overall, there are few patients with RRP in patients categorised as in remission or LDA by all composite scores. Differences in disease activity between treatment arms (eg, treatment groups 1 and 2 vs 3 and 4) could be confirmed with all indices.

**DISCUSSION**

The original DAS is sometimes criticised for being complicated because it includes the RAI. We compared three alternatives with the original DAS, with various tender joint...
A limitation of the current study is caused by the rapid reduction in disease activity in DAS nor in the original DAS28. RRP were not influenced by the use of VAS–PGA or VAS–GH, neither in the alternative of these scores. Differences are nonetheless very small. The percentages of patients with corresponding higher classification leads to less radiological damage in the HDA group. The slightly higher disease activity measured with both DAS TJC44 and DAS TJC53 with patients with RRP in DAS28 remission was higher compared with the (alternative) DAS. This can be explained because both DAS TJC53 and DAS TJC44 assess more joints separately, classifying more MDA and HDA, less LDA and similar remission percentages. This can be explained because both DAS TJC53 and DAS TJC44 assess more joints separately, causing a small shift to a higher disease activity category. However, the vast majority of patients assessed as being in remission and consequently a smaller LDA group, and thus remission percentages, remain the same. DAS28 shows a different pattern with remission patients have none to one painful joint in which disease activity by any score, causing a small shift to a higher disease activity category. However, the vast majority of patients; however, for some individual patients differences between scores may be larger.

In conclusion, we have shown that scoring the presence or absence of tenderness in individual joints to calculate a disease activity score performs as well as scoring a graded tenderness score in joint groups. In daily practice or clinical studies, using a DAS alternative may be much easier than the original DAS with RAI. The score based on the assessment of tenderness in the same 44 joints assessed for swelling may be most practical.

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Chapter 7

Association with joint damage and physical functioning of nine composite indices and the 2011 ACR/EULAR remission criteria in rheumatoid arthritis


*both authors contributed equally

Ann Rheum Dis 2011; 70: 1815-1821
ABSTRACT

Objective: To compare nine disease activity indices and the new American College of Rheumatology (ACR)/European League against Rheumatism (EULAR) remission criteria in rheumatoid arthritis (RA) and to relate these to physical function and joint damage progression.

Methods: Five-year data from the BeSt study were used, a randomised clinical trial comparing four treatment strategies in 508 patients with recent-onset RA. Every three months disease activity was assessed with nine indices (Disease Activity Score (DAS), DAS-C reactive protein (DAS-CRP), Disease Activity Score in 28 joints (DAS28), DAS28-CRP, Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI) and three DAS versions with adjusted tender scores) and categorised into remission, low, moderate and high disease activity (LDA, MDA, HDA). In addition, ACR/EULAR clinical trial and practice remission was assessed 3-monthly with 28 and 68/66 joint counts. For each index, Generalized Estimating Equations analyses were performed to relate disease activity levels and the absence/presence of remission to 3-monthly assessments of physical functioning and annual radiological progression.

Results: From the composite indices, CDAI and SDAI were the most stringent definitions of remission and classified more patients as LDA. DAS28 and DAS28-CRP had the highest proportions of remission and MDA and a smaller proportion of LDA. ACR/EULAR remission percentages were comparable to CDAI/SDAI remission percentages. The variant including CRP and 68/66 joint counts was the most stringent. For all indices, higher levels of disease activity were associated with decreased functioning and more radiological damage progression. Despite differences in classification between the indices, no major differences in relation to the two outcomes were observed.

Conclusion: The associations of nine composite indices and ACR/EULAR remission criteria with functional status and joint damage progression showed high accordance, whereas the proportions of patients classified in the disease activity levels differed.

INTRODUCTION

Assessing disease activity and the response to treatment is of vital importance in rheumatoid arthritis (RA), both in clinical trials and in daily practice. By early and effective suppression of inflammation, severe joint destruction and functional disability can be prevented. The use of a tightly controlled treatment approach, including frequent disease activity measurements and treatment towards a preset goal, have further improved outcomes. In order to measure disease activity, several composite scores have been developed such as the Disease Activity Score (DAS), Disease Activity Score in 28 joints (DAS28), the Clinical Disease Activity index (CDAI) and the Simplified Disease Activity Index (SDAI) as a combination of variables might represent actual disease activity better than single measures. We recently validated three new variants of the original DAS with adjusted tender joint counts (TJCs).

All composite scores on continuous scales can be subdivided into categories (remission, low disease activity (LDA), moderate disease activity (MDA) and high disease activity (HDA)), which nowadays are also being used as tools to guide treatment decisions for individual patients. Beside these index-based criteria, an international taskforce from the American College of Rheumatology (ACR) and the European League against Rheumatism (EULAR) recently developed new remission criteria for clinical practice and clinical trials.

In previous studies the number of indices compared, patient numbers or duration of follow-up duration were limited and few studies related disease activity levels to functional ability or radiological damage progression in time. Little is known about the performance of the new ACR/EULAR remission criteria in comparison with existing index-based remission definitions. To be able to compare the results of registries or clinical trials reliably using different composite scores, a more extended comparison is needed. The aims of this study were: (1) to compare the classification of disease activity according to nine composite scores into remission, low disease activity (LDA), moderate disease activity (MDA) and high disease activity (HDA)), which nowadays are also being used as tools to guide treatment decisions for individual patients. Beside these index-based criteria, an international taskforce from the American College of Rheumatology (ACR) and the European League against Rheumatism (EULAR) recently developed new remission criteria for clinical practice and clinical trials.

The variant including CRP and 68/66 joint counts was the most stringent. For all indices, higher levels of disease activity were associated with decreased functioning and more radiological damage progression. Despite differences in classification between the indices, no major differences in relation to the two outcomes were observed.

Conclusion: The associations of nine composite indices and ACR/EULAR remission criteria with functional status and joint damage progression showed high accordance, whereas the proportions of patients classified in the disease activity levels differed.

METHODS

Patients

Five-year follow-up data of the BeSt study were used in which 508 patients with recent-onset rheumatoid arthritis with a disease duration ≤2 years were randomised into four dynamic treatment strategies: 1) sequential monotherapy; 2) step-up combination therapy; 3) initial combination therapy with prednisone and 4) initial combination therapy with infliximab. Details have been described elsewhere. Treatment was adjusted based on 3-monthly measurements of disease activity. If DAS was >2.4, the next step of the protocol was taken. If DAS was ≤2.4 for ≥6 months, the medication was tapered to monotherapy in a maintenance dose. From the third year the last dis-
ease-modifying antirheumatic drug (DMARD) could be tapered and discontinued if DAS was <1.6 for 26 months in patients on monotherapy at the maintenance dose. The last DMARD was restarted if DAS was ≥1.6.

Clinical assessments
Every three months the following variables were collected: 66 swollen joint count (SJC), 68 TJC, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), patient’s assessment of global health (VAS-GH) on a visual analogue scale (0-100 mm) and physician’s global assessment of disease activity (VAS-PGA).

At each timepoint disease activity was calculated according to the following composite indices (Table 1): the original DAS with ESR or CRP (DAS, DAS-CRP), DAS28 with ESR or CRP (DAS28, DAS28-CRP), SDAI, CDAI, and three variants of the original DAS with adjustments in the TJC of the score. In the first adjustment (DAS 0-1) the same joints and joint groups were used as in the Ritchie Articular Index (RAI) but scoring only absence (0) or presence (1) of tenderness instead of grading tenderness from 0 to 3. In the second adjustment version (DAS-TJC53), grading and assessment of joint groups were omitted: all 53 joints of the RAI counted separately for the absence or presence of tenderness. In the last version only the 44 joints (equal to the joints assessed for swelling) were assessed for the absence or presence of tenderness (DAS-TJC44). Furthermore, the presence or absence of ACR/EULAR remission was assessed using the following components: SJC ≤5, TJC ≤1, VAS-GH ≤1 cm and CRP ≤0.5 g/dl. Four variants were used: a clinical trial definition including CRP and a clinical practice definition excluding CRP, each with a 28/28 SJC/TJC and with a 68/66 SJC/TJC.

At each timepoint patients were classified as being in remission (yes/no) according to nine composite indices and ACR/EULAR remission criteria, or in LDA, MDA or HDA according to nine composite indices based on previously published cut-off points (Table 1). For the three simplifications of the original DAS, the cut-off points of the original DAS were used.

Outcome assessments
Every 3 months functional capacity was assessed using the health assessment questionnaire (HAQ). Joint damage was assessed on annual x-rays from baseline until year 5 per patient in random order using the Sharp-van der Heijde method by two independent readers blinded to patient identity. The mean scores of the two readers were used.

Statistical analysis
SPSS Version 17.0 was used for all analyses. To assess the relationship between the level of disease activity according to the nine disease activity indices, ACR/EULAR remission criteria and HAQ, four Generalised Estimating Equations (GEE) analyses were performed per index, first with HAQ per patient as a continuous outcome and with HAQ per patient as a dichotomous outcome for three cut-off points (HAQ >1.0, HAQ >0.5, HAQ >0).

The disease activity level was added as an explanatory variable categorised as remission, LDA, MDA and HDA, or as remission yes/no. All analyses were corrected for baseline HAQ, time, age, gender and treatment group with additional correction for time*time in the continuous HAQ analysis to approach linearity. For each disease activity level (remission, LDA, MDA, HDA or remission yes/no) and per composite score the mean HAQ scores (continuous outcome) and probabilities of an HAQ score above the cut-off point (dichotomous outcome) were estimated within the GEE model. For this purpose the Estimated Marginal Means subcommand was used which fills in the regression equation by fixing continuous values of covariates at their means and estimates HAQ values for each level of a categorical variable. This option was used to avoid differences in distribution of confounders between different disease activity levels and composite scores.

To assess the relationship between the level of disease activity according to the different composite indices, ACR/EULAR remission and the progression of joint damage, four GEE analyses were performed for each composite index: first with the absolute annual Sharp-van der Heijde progression score (SHS) progression per year as a continuous outcome and then with the annual SHS progression as a dichotomous outcome (cut-off points >2, >2 and ≤5 SHS units progression per year). Since x-rays were taken annually and disease activity was measured every three months, for the analysis including composite scores only the mean disease activity per year was calculated by the following formula: \( \frac{0.5 \times \text{DAS}_1 + \text{DAS}_2 + \text{DAS}_3 + \text{DAS}_4 + 0.5 \times \text{DAS}_5}{4} \) and categorised into remission, LDA, MDA and HDA. For single missing values we used a last observation carried forward method before calculating mean disease activity per year. This categorical mean

<table>
<thead>
<tr>
<th>Formula</th>
<th>Remission LDA MDA HDA</th>
</tr>
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<tbody>
<tr>
<td>DAS 0-1 0.5589(VASphysician [mm]) + 0.0142(VASpatient [mm]) + 0.3310ln(ESR) + 0.00722(VASpatient [mm])</td>
<td>&lt;1.6 216 and 21.6 ≥2.6 and ≤3.2 &gt;3.2 and ≤5.1 &gt;5.1</td>
</tr>
<tr>
<td>DAS CRP 0.569(VASphysician [mm]) + 0.0142(VASpatient [mm]) + 0.3310ln(ESR) + 0.00722(VASpatient [mm])</td>
<td>&lt;1.6 216 and 21.6 ≥2.6 and ≤3.2 &gt;3.2 and ≤5.1 &gt;5.1</td>
</tr>
<tr>
<td>DAS28 0.569(VASphysician [mm]) + 0.0142(VASpatient [mm]) + 0.3310ln(ESR) + 0.00722(VASpatient [mm])</td>
<td>&lt;1.6 216 and 21.6 ≥2.6 and ≤3.2 &gt;3.2 and ≤5.1 &gt;5.1</td>
</tr>
<tr>
<td>DAS CRP 0.569(VASphysician [mm]) + 0.0142(VASpatient [mm]) + 0.3310ln(ESR) + 0.00722(VASpatient [mm])</td>
<td>&lt;1.6 216 and 21.6 ≥2.6 and ≤3.2 &gt;3.2 and ≤5.1 &gt;5.1</td>
</tr>
<tr>
<td>DAS TJC44 + VASphysician [cm] + VASpatient [cm] + CRP (mg/dl)</td>
<td>≤2.8 218 and 21.8 &gt;2.8 and ≤10 &gt;10 and ≤22 &gt;22</td>
</tr>
<tr>
<td>DAS TJC53 + VASphysician [cm] + VASpatient [cm] + CRP (mg/dl)</td>
<td>≤2.8 218 and 21.8 &gt;2.8 and ≤10 &gt;10 and ≤22 &gt;22</td>
</tr>
<tr>
<td>DAS 0-1 0.5589(VASphysician [mm]) + 0.0142(VASpatient [mm]) + 0.3310ln(ESR) + 0.00722(VASpatient [mm])</td>
<td>&lt;1.6 216 and 21.6 ≥2.6 and ≤3.2 &gt;3.2 and ≤5.1 &gt;5.1</td>
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</tr>
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<td>DAS TJC53 + VASphysician [cm] + VASpatient [cm] + CRP (mg/dl)</td>
<td>≤2.8 218 and 21.8 &gt;2.8 and ≤10 &gt;10 and ≤22 &gt;22</td>
</tr>
</tbody>
</table>

LDA, low disease activity; MDA, moderate disease activity; HDA, high disease activity; DAS, disease activity score; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; DAS28, disease activity score in 28 joints; SDAI, simplified disease activity index; CDAI, clinical disease activity index; DAS 0-1, disease activity score with ‘Ritchie articular index’ without grading; TJC53, tender joint count in 53 joints; TJC44, tender joint count in 44 joints RAI, Ritchie articular index; SJC44, swollen joint count in 44 joints; SJC28; patient’s assessment of global health on a visual analogue scale; TJC28, tender joint count in 28 joints; SJC28; swollen joint count in 28 joints; VASphysician, physician’s assessment of disease activity on a visual analogue scale.

LDA, MDA and HDA, or as remission yes/no. All analyses were corrected for baseline HAQ, time, age, gender and treatment group with additional correction for time*time in the continuous HAQ analysis to approach linearity. For each disease activity level (remission, LDA, MDA, HDA or remission yes/no) and per composite score the mean HAQ scores (continuous outcome) and probabilities of an HAQ score above the cut-off point (dichotomous outcome) were estimated within the GEE model. For this purpose the Estimated Marginal Means subcommand was used which fills in the regression equation by fixing continuous values of covariates at their means and estimates HAQ values for each level of a categorical variable. This option was used to avoid differences in distribution of confounders between different disease activity levels and composite scores. To assess the relationship between the level of disease activity according to the different composite indices, ACR/EULAR remission and the progression of joint damage, four GEE analyses were performed for each composite index first with the absolute annual Sharp-van der Heijde progression score (SHS) progression per year as a continuous outcome and then with the annual SHS progression as a dichotomous outcome (cut-off points >1, >2 and ≤5 SHS units progression per year). Since x-rays were taken annually and disease activity was measured every three months, for the analysis including composite scores only the mean disease activity per year was calculated by the following formula: \( \frac{0.5 \times \text{DAS}_1 + \text{DAS}_2 + \text{DAS}_3 + \text{DAS}_4 + 0.5 \times \text{DAS}_5}{4} \) and categorised into remission, LDA, MDA and HDA. For single missing values we used a last observation carried forward method before calculating mean disease activity per year. This categorical mean
Chapter 7 A comparison of composite indices and remission criteria

Disease activity level per year or remission yes/no was added as an explanatory variable. Remission per year was defined as ≥2/4 visits remission.

The SHS analyses were corrected for total SHS at the beginning of each year, time, presence of cyclic citrullinated peptides (CCP) antibodies, treatment group, age and gender. Mean progression scores and probabilities for progression were estimated for index and each disease activity level using estimated marginal means.

The GEE method with M-dependence covariance structure was used to correct for within-patient correlation since HAQ and joint damage progression was repeated measured over time.

RESULTS

At baseline, patients (n=508) had active disease with a mean (SD) DAS of 4.4 (0.9) and a mean (SD) HAQ of 1.4 (0.9). Mean (SD) / median (IQR) SHS at baseline was 7.1 (10.2) / 3.0 (0.5 – 9.5).

Spider diagrams

Spider diagrams (figure 1 A,B) illustrate the classification in disease activity categories according to the different composite indices. Irrespective of the composite score used, more patients were classified in HDA categories in year 1 than in year 5, reflecting treatment efficacy. From the composite indices, CDAI and SDAI had the most stringent definitions of remission and thus classified a relatively high proportion of patients in the LDA category. The proportions of patients in MDA and HDA were comparable between CDAI, SDAI, DAS and DAS-CRP. DAS28 and DAS28-CRP had the highest proportions remission and MDA and a relatively small proportion of patients in LDA. Of the adjusted DAS versions, DAS 0-1 was very comparable with the original DAS. The absolute DAS-TJC53 and, to a lesser extent, the DAS-TJC44 were slightly higher than the original DAS, resulting in higher percentages of patients in the HDA. Figure 1 C,D show the remission percentages of the composite indices and ACR/EULAR remission criteria. The most stringent definition is the clinical trial definition with 66/68 joints. Clinical trial remission criteria show lower remission percentages than clinical practice remission criteria, as did the criteria including a full 68/66 joint count compared with the criteria based on 28-joint counts.

Relation with functional ability

In general, predicted HAQ values among the disease activity levels based on the composite indices showed high agreement (table 2). As expected, HAQ values are lower when the level of disease activity was lower. Although CDAI and SDAI classified fewer patients as being in remission, CDAI and SDAI remission was not associated with lower HAQ scores than other indices (table 2). Compared with other indices, DAS28 variants classified the highest proportion of patients in the remission and MDA categories, and fewer patients in LDA category, but HAQ levels in remission, LDA and MDA were com-

TABLE 2 Mean predicted HAQ for patients in remission, LDA, MDA and HDA. Covariates and factors appearing in the model are fixed at the following values: baseline HAQ 1.4, visit 10.6, age 53.9, treatment group 1, female gender.

<table>
<thead>
<tr>
<th>Remission</th>
<th>LDA</th>
<th>MDA</th>
<th>HDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (95% CI)</td>
<td>Mean (95% CI)</td>
<td>Mean (95% CI)</td>
<td>Mean (95% CI)</td>
</tr>
<tr>
<td>DAS</td>
<td>0.48 (0.39 – 0.56)</td>
<td>0.61 (0.53 – 0.69)</td>
<td>0.83 (0.75 – 0.91)</td>
</tr>
<tr>
<td>DAS CRP</td>
<td>0.49 (0.40 – 0.57)</td>
<td>0.64 (0.55 – 0.71)</td>
<td>0.87 (0.79 – 0.95)</td>
</tr>
<tr>
<td>DAS28</td>
<td>0.49 (0.40 – 0.57)</td>
<td>0.60 (0.51 – 0.68)</td>
<td>0.79 (0.70 – 0.88)</td>
</tr>
<tr>
<td>DAS28 CRP</td>
<td>0.52 (0.44 – 0.60)</td>
<td>0.62 (0.54 – 0.70)</td>
<td>0.80 (0.71 – 0.89)</td>
</tr>
<tr>
<td>SDAI</td>
<td>0.47 (0.39 – 0.55)</td>
<td>0.60 (0.51 – 0.68)</td>
<td>0.83 (0.75 – 0.90)</td>
</tr>
<tr>
<td>CDAI</td>
<td>0.46 (0.38 – 0.54)</td>
<td>0.60 (0.51 – 0.68)</td>
<td>0.83 (0.74 – 0.91)</td>
</tr>
<tr>
<td>DAS 0-1</td>
<td>0.48 (0.40 – 0.56)</td>
<td>0.61 (0.53 – 0.70)</td>
<td>0.84 (0.75 – 0.92)</td>
</tr>
<tr>
<td>DAS-TJC53</td>
<td>0.47 (0.39 – 0.55)</td>
<td>0.60 (0.51 – 0.68)</td>
<td>0.77 (0.69 – 0.83)</td>
</tr>
<tr>
<td>DAS-TJC44</td>
<td>0.48 (0.39 – 0.56)</td>
<td>0.60 (0.51 – 0.68)</td>
<td>0.78 (0.70 – 0.86)</td>
</tr>
</tbody>
</table>

CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS, Disease Activity Score; DAS 0-1, Disease Activity Score with RAI 0-1; DAS28, Disease Activity Score in 28 joints; HDA, high disease activity; LDA, low disease activity; MDA, moderate disease activity; SDAI, Simplified Disease Activity Index; TJC44, tender joint count 44 joints; TJC53, tender joint count 53 joints.

FIGURE 1 Spider diagrams showing the cumulative percentage of patients in remission, low, moderate and high disease activity according to the different composite indices at (A) 1 year (n=465) and (B) 5 year (n=508). Bar charts show the percentage of patients in remission (2) visits for (C) year 1 (n=242) and (D) year 5 (n=267) per remission definition. ACR, American College of Rheumatology; CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS, Disease Activity Score; DAS 0-1, Disease Activity Score with RAI 0-1; DAS28, Disease Activity Score in 28 joints; HDA, high disease activity; LDA, low disease activity; MDA, moderate disease activity; SDAI, Simplified Disease Activity Index; TJC44, tender joint count 44 joints; TJC53, tender joint count 53 joints.
parable to other indices. Patients in HDA according to the DAS-TJC53 and DAS-TJC44 have lower HAQ scores than patients in HDA according to other indices. Similar results were seen with regard to the probability of a HAQ score >0.5 as outcome (Table 3). Overall, 34-91% of patients were limited in functioning depending on their disease activity level. HDA corresponds with a higher chance of functional limitations. In general there was little difference between the percentages of HAQ scores >0.5 for all composite scores, but the same subtle differences were found as were seen previously. In the analysis including ACR/EULAR remission definitions, the same pattern was found (Table 6). Predicted HAQ scores and probabilities for a HAQ score >0.5 were comparable for all definitions, with SDAI, CDAI and ACR/EULAR remission at the lower end of range. Very little difference was found within the group of ACR/EULAR remission definitions.

Relation to the progression of joint damage

Table 4 shows predicted values of SHS progression for patients in different disease activity levels according to the nine indices. All indices showed similar joint damage progression in different disease activity levels, and all composite indices showed a dose response with a higher level of disease activity levels yielding more joint damage progression. Although CDAI and SDAI classified fewer patients as being in remission, CDAI and SDAI remission were not associated with less damage progression. In the HDA category, patients with DAS-TJC53 and DAS-TJC44 had somewhat less SHS progression than patients in HDA according to other indices (Table 4).

Predicted probabilities for SHS progression ≥3 units for patients in remission, LDA, MDA and HDA categories according to the nine indices are shown in Table 5. The proportions of SHS progression between different composite indices were very comparable. The percentage of CCP-positive female patients in remission showing joint damage progression varies between 9% and 12% for progression of ≥3 units (Table 5). The chance of progression ≥3 units in CCP-negative patients in remission was lower (3-4% SHS progression ≥3 units, data not shown). Patients in SDAI and CDAI remission had comparable chances of progression of ≥3 units as other indices (9% vs 9-12%). The probability for progression of ≥3 units in the LDA category was slightly lower with SDAI, CDAI and DAS28 than with other indices. The four versions of the ACR/EULAR remission criteria were comparably related to joint damage progression (Table 6). The probability of annual SHS progression of ≥3 units for patients in remission was 9-12% compared with 24-28% for patients not
in remission. Probabilities for progression as well as absolute SHS progression values were comparable for all definitions. Comparable patterns were seen for annual SHS progression of 21 and 25 units (data not shown).

**DISCUSSION**

We compared classification into remission, LDA, MDA and HDA or remission yes/no with nine composite disease activity scores and ACR/EULAR remission criteria and assessed the relationship with functional ability and radiological damage progression. Although the proportions of patients classified varied between some of disease activity levels and definitions, the associations of all composite scores and remission definitions with HAQ and SHS showed overall high agreement. All showed a good dose-response relationship of disease activity with HAQ and SHS progression. This analysis expands on earlier studies comparing composite indices. We compared composite scores including 28-joint counts and also the original DAS and several adjustments. Previous studies showed that DAS28 classifies more patients in remission,\(^{17,26}\) while SDAI and CDAI are more strict in classifying remission\(^{27,28}\) as reflected by lower remission percentages, which is in line with our results. In general, the studies that link composite scores to functional ability and radiological progression show that DAS28, SDAI and CDAI correlate comparable with HAQ and Larsen scores. They demonstrate that levels of disease activity of these indices discriminate between levels of functional state and radiological damage.\(^{30,32}\) We showed that all nine composite indices had a comparable relationship with radiological joint damage or physical functioning. Omitting grading in TJC\(s\) and/or omitting scoring tender joints in joint groups did not change this relationship. The same is true if acute phase reactants are left out (CDAI and clinical trial ACR/EULAR remission criteria). Which index should be preferred will depend on the reason for using the index and on personal preferences. In clinical practice, composite scores without an acute phase reactant or a limited joint count can be used whereas, in a clinical trial setting, a more elaborate composite score can be valuable. If treatment is aimed at remission, strict remission criteria carry a higher risk of overtreatment. However, a less strict definition may lead to residual disease activity and thereby undertreatment. SDAI, CDAI and ACR/EULAR remission criteria classified the lowest proportion of patients in remission than the other indices but were not associated with lower HAQ scores and did not lead to clinically significant less joint damage progression. DAS28 and DAS28-CRP classified the highest proportion of patients in clinical remission without compromising on HAQ and joint damage progression. However, within these indices patients’ feet are not examined, which may not be appreciated. If LDA should be the target, DAS28 variants may be less useful because DAS28 and DAS28-CRP classified fewer patients in LDA and remission together than other indices without leading to better HAQ and less joint damage progression. Our results emphasise earlier reports that clinical remission does not necessarily coincide with radiological remission.\(^{30,31}\) The predicted probability for joint damage progression (23 units) was 9–12% in anti-CCP-positive patients. This suggests that there is (sub) clinical inflammation in patients in clinical remission, even with stricter definitions. An additional explanation might be that there is a delay between inflammation measured with clinical parameters and progression of joint damage visible on conventional x-rays. Part of the joint damage progression seen in patients in clinical remission might reflect disease activity that was present before the onset of clinical remission.\(^{15}\) Our results emphasise that a comprehensive definition of disease remission needs to include radiological outcome.

| Table 6 | Estimated mean predicted HAQ scores and mean SHS progression scores and estimated probability for HAQ scores >0.5 and SHS progression ≥5 units in patients in remission versus no remission. Covariates and factors appearing in the HAQ model are fixed at the following values: baseline HAQ 1.2; visit 10.6; age 53.9; treatment group 1; female gender. Covariates and factors appearing in the SHS model are fixed at the following values: previous SHS 10.3; year 2.8; age 53.8; treatment group 1; anti-CCP positive patients; female gender. |
|-----------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| **HAQ >0.5** | **Absolute HAQ value** | **SHS ≥5.0** | **Absolute SHS value** |
| Remission | No remission | Remission | No remission | Remission | No remission | Remission | No remission | Remission | No remission | Remission | No remission |
| Probability (95% CI) | Mean (95% CI) | Probability (95% CI) | Mean (95% CI) | Probability (95% CI) | Mean (95% CI) | Probability (95% CI) | Mean (95% CI) | Probability (95% CI) | Mean (95% CI) |
| **DAS** | | | | | | | | | | | |
| 0.65 | (0.56 – 0.72) | 0.47 | (0.39 – 0.53) | 0.69 | (0.62 – 0.75) | 0.39 | (0.32 – 0.45) | 0.40 | (0.32 – 0.50) | 0.63 | (0.55 – 0.70) |
| **DAS CRP** | | | | | | | | | | | |
| 0.71 | (0.63 – 0.79) | 0.50 | (0.42 – 0.57) | 0.74 | (0.66 – 0.82) | 0.42 | (0.34 – 0.50) | 0.43 | (0.35 – 0.50) | 0.75 | (0.67 – 0.83) |
| **DAS TJC44** | | | | | | | | | | | |
| 0.68 | (0.59 – 0.77) | 0.47 | (0.39 – 0.55) | 0.71 | (0.63 – 0.79) | 0.41 | (0.33 – 0.49) | 0.42 | (0.34 – 0.49) | 0.73 | (0.65 – 0.81) |
| **DAS TJC48** | | | | | | | | | | | |
| 0.69 | (0.61 – 0.77) | 0.47 | (0.39 – 0.55) | 0.71 | (0.63 – 0.79) | 0.41 | (0.33 – 0.49) | 0.42 | (0.34 – 0.49) | 0.73 | (0.65 – 0.81) |
| **ACR 28** | | | | | | | | | | | |
| 0.70 | (0.61 – 0.79) | 0.48 | (0.40 – 0.56) | 0.72 | (0.64 – 0.80) | 0.41 | (0.33 – 0.49) | 0.42 | (0.34 – 0.49) | 0.73 | (0.65 – 0.81) |
| **ACR 68/66** | | | | | | | | | | | |
| 0.69 | (0.61 – 0.78) | 0.47 | (0.39 – 0.55) | 0.71 | (0.63 – 0.79) | 0.41 | (0.33 – 0.49) | 0.42 | (0.34 – 0.49) | 0.73 | (0.65 – 0.81) |
| **ACR 28 trial** | | | | | | | | | | | |
| 0.70 | (0.61 – 0.80) | 0.48 | (0.40 – 0.56) | 0.72 | (0.64 – 0.80) | 0.41 | (0.33 – 0.49) | 0.42 | (0.34 – 0.49) | 0.73 | (0.65 – 0.81) |
| **ACR 68/66 trial** | | | | | | | | | | | |
| 0.70 | (0.61 – 0.80) | 0.48 | (0.40 – 0.56) | 0.72 | (0.64 – 0.80) | 0.41 | (0.33 – 0.49) | 0.42 | (0.34 – 0.49) | 0.73 | (0.65 – 0.81) |
| **ACR 28 practice** | | | | | | | | | | | |
| 0.69 | (0.61 – 0.80) | 0.47 | (0.39 – 0.55) | 0.71 | (0.63 – 0.79) | 0.41 | (0.33 – 0.49) | 0.42 | (0.34 – 0.49) | 0.73 | (0.65 – 0.81) |
| **ACR 68/66 practice** | | | | | | | | | | | |
| 0.70 | (0.61 – 0.80) | 0.48 | (0.40 – 0.56) | 0.72 | (0.64 – 0.80) | 0.41 | (0.33 – 0.49) | 0.42 | (0.34 – 0.49) | 0.73 | (0.65 – 0.81) |
| **ACR 28 practice** | | | | | | | | | | | |
| 0.70 | (0.61 – 0.80) | 0.48 | (0.40 – 0.56) | 0.72 | (0.64 – 0.80) | 0.41 | (0.33 – 0.49) | 0.42 | (0.34 – 0.49) | 0.73 | (0.65 – 0.81) |

ACR, American College of Rheumatology; CCP, cyclic citrullinated peptide; CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS, Disease Activity Score; DAS 28, Disease Activity Score with RA1 0-1; DAS28, Disease Activity Score in 28 joints; SDAI, Simplified Disease Activity Index; SHS, Sharp-van der Heijde score; TJC44, tender joint count 44 joints; TJC27, tender joint count 27 joints.

Previous studies have shown that, early in the disease course active inflammation (reflected in composite indices) is the main determinant of functional limitations while, in more established disease, joint damage becomes more important.\textsuperscript{1,3,4} We analysed the association between disease activity levels and HAQ in patients with limited joint damage during a 5-year follow-up period. In more advanced disease the dose response between disease activity levels and HAQ is probably less pronounced and/or HAQ values among remission patients may be higher.

There is a large body of evidence supporting the benefit of targeted treatment. Less is known on what the target should be.\textsuperscript{4,5,6} RCTs directly comparing LDA and remission are lacking. In the BeSt study treatment was aimed at LDA. There is little difference between the mean HAQ in LDA (\textasciitilde 0.60) and in remission (\textasciitilde 0.50). However, progression rates in patients in LDA are considerably higher than those patients in remission, suggesting that treatment should aim at remission. It is not known what the gain would be on clinical and radiological outcomes while risking higher turnover in treatment options.

When outcomes are dichotomised, only part of the data is being used, in contrast to using data on a continuous scale. Joint damage progression, (and, to a lesser extent HAQ) does not follow a Gaussian distribution. Although the GEE method is relatively robust against violations of the normal distribution, it is impossible to disentangle the complete effect of the distribution on continuous outcomes and predicted treatment group. This may explain part of the high predicted annual progression rate, which can also be explained by unfavourable characteristics like anti-CCP positivity and treatment group. With dichotomous outcomes, the distribution is not a problem. Therefore we decided to show both.

The strengths of our study are that we compared the most widely used composite indices for RA and recently published ACR/EULAR remission criteria with different joint counts and related the classification of these indices to HAQ and joint damage progression (SHS) in a large group of patients. Also, all indices/criteria were repeatedly measured over time, increasing the number of observations, and were incorporated in the GEE analyses. One limitation might be that ‘old’ ACR remission criteria were not included in the analyses as not all components of these criteria were gathered 3-monthly.

In conclusion, although there are differences in classification between 9 different disease activity composite indices and ACR/EULAR remission definitions for RA, the associations with functional status and joint damage progression are highly comparable. The choice of composite index is dependent on its intended use.

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Discontinuation of infliximab and potential predictors of persistent low disease activity

M. van den Broek, N.B. Klarenbeek, L. Dirven, D. van Schaardenburg, H.M.J. Hulsmans, P.J.S.M. Kerstens, T.W.J. Huizinga, B.A.C. Dijkmans, C.F. Allaart

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Chapter 8 Discontinuation of infliximab and potential predictors of persistent low disease activity

ABSTRACT

Objective: To describe the disease course after the cessation of infliximab in early rheumatoid arthritis patients with disease activity score (DAS)-steered treatment and to identify predictors of persistent low disease activity.

Methods: In a post-hoc analysis of the BeSt study, disease activity and joint damage progression were observed in patients treated with methotrexate plus infliximab, who discontinued infliximab after achieving low disease activity (DAS ≤2.4) for 6 months. Predictors were identified using Cox regression analysis.

Results: 104 patients discontinued infliximab, of whom 77 had received infliximab plus methotrexate as initial treatment. Mean DAS at the time of infliximab cessation was 1.3, median symptom duration was 23 months and median Sharp-van der Heijde score was 5.5. The median follow-up was 7.2 years. Infliximab was re-introduced after loss of low disease activity in 48%, after a median of 17 months. The joint damage progression rate did not increase in the year after cessation, regardless of flare. After re-introduction of infliximab, 84% of these patients again achieved a DAS ≤2.4. In the multivariable model, smoking, infliximab treatment duration ≥18 months and shared epitope (SE) were independently associated with the re-introduction of infliximab: 6% of the non-smoking, SE-negative patients treated <18 months needed infliximab re-introduction.

Conclusion: Cessation of infliximab was successful in 52%, with numerically higher success rates in patients initially treated with infliximab. Of the 48% who flared, 84% regained low disease activity. The joint damage progression rate did not increase in the year after cessation. Smoking, long infliximab treatment duration and SE were independently associated with re-introduction of infliximab.

INTRODUCTION

Current rheumatoid arthritis (RA) treatment strategies are aimed at achieving low disease activity as soon as possible, to improve structural and functional outcome, using frequent treatment adjustments when necessary. Adding a tumour necrosis factor (TNF) blocker to methotrexate has proved to be an effective way to achieve low disease activity in a short period of time, with less joint damage progression than mono-therapy. Treatment with TNF blockers is expensive and has a possible risk of adverse events. Therefore, discontinuation of TNF blockers once the treatment goal has been achieved could be beneficial for both society and individual patients. In 25–70% of patients who achieved low disease activity, TNF blockers could be stopped without losing low disease activity. Predicting which patients have a high chance of sustained low disease activity after the cessation of TNF blockers is necessary to avoid disease flares and a potentially increased risk of infusion reactions after the re-introduction of intravenous TNF blockers.

In the BeSt study, a study comparing four different treatment strategies, infliximab was the TNF blocker used in combination with methotrexate, either after failure on at least three non-biological disease-modifying antirheumatic drugs (DMARD), or as initial treatment. In this post-hoc analysis with a median follow-up duration of 7.2 years, we investigated whether and how often low disease activity was sustained after the cessation of infliximab and if predictors for successful cessation exist. Second, we looked at joint damage progression after infliximab cessation and we assessed the success and safety of re-introduction.

METHODS

Patients

Between 2000 and 2002, 508 patients were included in the BeSt study, a multicentre randomised single blind clinical trial designed to compare four different treatment strategies in DMARD-naive patients with recent-onset, active RA. All patients fulfilled the 1987 American College of Rheumatology classification criteria for RA. The ethics committees of all participating centres approved the study protocol and patients gave their written informed consent.

Treatment strategies were sequential monotherapy, step-up combination therapy (groups 1 and 2, both starting with methotrexate), initial combination therapy with methotrexate, sulfasalazine and prednisone (group 3) and initial combination therapy with methotrexate and infliximab (group 4). Treatment was adjusted to the next step in the protocol in the case of a disease activity score (DAS) greater than 2.4 or side effects. In groups 1–3, methotrexate plus infliximab were started after patients had failed on three treatment steps with non-biological DMARD including prednisolone (groups 2 and 3) or without (group 1). If the DAS remained at 2.4 or less for at least 6 months,
infliximab was stopped, after stepwise (10–7.5–6–3) tapering to 3 mg/kg per 8 weeks in those patients who had previously had a dose increase. Infliximab was immediately restarted if the DAS increased to over 2.4. In patients who had also tapered or stopped methotrexate, first methotrexate was increased to 25 mg/week. Next, infliximab was re-introduced if the DAS remained greater than 2.4. The complete study design has been published previously.9,10 We analysed all 104 patients in groups 1–4 who discontinued infliximab after the DAS was 2.4 or less for 6 months, who had at least one year of follow-up after reaching this point. The median follow-up duration from the time of infliximab discontinuation was 7.2 years (range 14–103 months).

Study endpoints
After cessation of infliximab, whether patients had to restart infliximab due to a DAS greater than 2.4 was monitored. Radiographs of the hands and feet were taken at yearly intervals. For the x-ray ‘at cessation’, the x-ray taken closest to the visit at cessation was used. For stop visits in between 2 yearly visits, the yearly visit before cessation was chosen. All available x-rays of the hands and feet, from baseline and 1, 2, 3, 4 and 5 year follow-up were scored blind for patient identity and random in time using the Sharp-van der Heijde score (SHS). Joint damage progression in the year before and after cessation was defined as an increase in the average score for those years of two independent readers. Smokers were defined as patients smoking cigarettes, cigars or a pipe at baseline.

Statistical analysis
Baseline and disease characteristics were compared between patients from the initial and the delayed infliximab treatment group, using the X2, Student’s t or Mann–Whitney U test. Joint damage progression and health assessment questionnaire (HAQ) scores were compared for patients with sustained DAS of 2.4 or less and patients who had to restart infliximab using the X2 and Mann–Whitney U test. To compare damage progression in the years before and after cessation and HAQ scores at and after cessation, the Wilcoxon signed-rank test was used. To take into account the difference in follow-up after cessation between patients, we used Cox regression analyses to identify predictors of successful cessation, after verifying that the proportional hazards assumption was not violated.11 The dependent variable was time to the re-introduction for patients who had to restart infliximab, whether this would significantly improve the model likelihood.11

RESULTS
Low disease activity
Infliximab was discontinued after achieving a DAS of 2.4 or less for 6 months or longer in 104 patients (figure 1): 77/120 from the initial infliximab treatment group and 27/109 from the delayed treatment group (p<0.001). The mean DAS at the time of cessation was 1.3 ± 0.6 (SD). The median infliximab treatment duration was 11 months (IQR 9–17). The median symptom duration at the time of cessation was 23 months (IQR 15–33). In 20 patients the infliximab dose had been increased from 3 to 6 mg/kg, to 7.5 mg/kg in 13 patients and to 10 mg/kg in five patients before a DAS of 2.4 or less was achieved. After the cessation of infliximab, the DAS remained 2.4 or less in 43/77 patients (56%) from the initial treatment group and 11/27 (41%) from the delayed treatment group. Methotrexate was then successfully tapered (with 2.5 mg every 4 weeks) to a maintenance dose (≤10 mg/week) in 34 patients (62%), without differences between the initial and delayed treatment groups (p=0.58). Subsequently, 15 patients (27%) from the initial treatment group achieved drug-free remission. None in the delayed treatment group achieved drug-free remission yet.

Treatment group
In the delayed treatment group, the median (IQR) time from baseline to starting infliximab was 14 months. Patients in the delayed treatment group had a higher baseline DAS and needed longer infliximab treatment before infliximab could be discontinued.

![Flowchart of the study](image-url)

FIGURE 1 Flowchart of the study. DAS, disease activity score; IFX, infliximab

hypothesised to have additional predictive value were added one by one. Model fit was tested using Martingale residuals. Overall goodness of fit was examined by adding to the model risk groups, constructed by categorising the ranked prognostic indices, to test whether this would significantly improve the model likelihood.11
than patients in the initial treatment group. At the time of infliximab discontinuation, patients in the delayed treatment group had longer symptom duration and a higher SHS, HAQ and patient’s assessment of disease activity. There were almost twice as many smokers in the delayed treatment group (table 1).

<table>
<thead>
<tr>
<th>TABLE 1 Patient demographic and disease characteristics at inclusion and at cessation of infliximab in the initial versus delayed infliximab treatment group.</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (n=104)</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>Female gender (n (%))</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>RF positive (n (%))</td>
</tr>
<tr>
<td>ACPA positive (n (%))</td>
</tr>
<tr>
<td>SE positive (n (%))</td>
</tr>
<tr>
<td>Smoking positive (n (%))</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
</tr>
<tr>
<td>IFX treatment duration at cessation (months)</td>
</tr>
<tr>
<td>HAQ at inclusion (mean (SD))</td>
</tr>
<tr>
<td>Remission at cessation (n (%))</td>
</tr>
<tr>
<td>SHS at cessation</td>
</tr>
</tbody>
</table>

Data are presented as median (IQR) unless stated otherwise.

Re-introduction of infliximab

In 50/104 patients (48%), infliximab was restarted after the DAS had increased to over 2.4 in a median of 17 months (IQR 3–47). Infliximab was discontinued for 1 year or more in 29 patients (58%). In 84%, 27/34 from the initial and 15/16 from the delayed infliximab treatment groups, a DAS of 2.4 or less was regained after the re-introduction of infliximab within a median 3 months (IQR 2–5). In five patients (10%), who had initially had a good response to re-introduction, infliximab was later abandoned for another DMARD. Five patients had an infusion reaction after the re-introduction of infliximab. These infusion reactions were reported as non-serious, but the reason for four patients to discontinue infliximab. In comparison, eight of 120 patients from the initial treatment group (group 4) of the BeSt study had an infusion reaction during their first treatment with infliximab (p=0.46). Serious infections (requiring hospital admission) occurred in 40/1000 patient-years after the re-introduction of infliximab, compared with 16/1000 patient-years during the first treatment with infliximab and 10/1000 patient-years during the cessation of infliximab.

Joint damage

Radiographs 1 year before, in the year of, and 1 year after infliximab cessation were available in 90/104 patients. Median damage progression was 0 both for patients who had an increase of the DAS to over 2.4 in the first year after cessation and patients whose DAS remained at 2.4 or less (p=0.56). The average damage progression did not increase in the year after cessation compared with the year before cessation: 0.0 (IQR 0.0–0.8) versus 0.0 (IQR 0.0–1.5), p=0.06. Four patients showed radiographic progression greater than 5 (figure 2). One of these patients had restarted infliximab in that year, the other three continued to have a DAS of 2.4 or less (mean area-under-the-curve DAS 2.0 in that year).

Functional ability after cessation

HAQ scores at 1 and 3 years after cessation were similar to HAQ scores at cessation in both restarters and patients with sustained DAS of 2.4 or less. Five years after cessation, restarters had a median HAQ of 0.7, versus 0.3 at cessation, p=0.02. For patients with sustained DAS of 2.4 or less, the median HAQ remained 0.1. Patients who flared in that year or the year before had higher median HAQ scores than patients who did not flare in those years: 0.4 versus 0.1 in year 1, 0.5 versus 0.1 in year 3 and 0.8 versus 0.4 in year 5, but these differences were not significant.

Predictors

Univariable Cox analyses showed that smoking, longer symptom duration at cessation, longer infliximab treatment duration, physician’s assessment of disease activity, total erosion score at the time of infliximab cessation and previous yearly change in SHS were associated with the re-introduction of infliximab (table 2). Treatment timing (delayed vs initial infliximab) and positivity for shared epitope (SE) showed a trend. Univariable
Table 3 Independent predictors of increase in DAS to greater than 2.4 with restart of infliximab (multivariable model)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Initial infliximab</th>
<th>Delayed infliximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>SE positive</td>
<td>3.5 (1.2 – 10.2)</td>
<td>3.7 (1.3 – 10.6)</td>
</tr>
<tr>
<td>Smoking</td>
<td>2.4 (1.3 – 4.6)</td>
<td>2.3 (1.3 – 4.2)</td>
</tr>
<tr>
<td>Treatment duration &gt; 24 months</td>
<td>2.4 (1.3 – 6.2)</td>
<td>2.1 (1.1 – 4.2)</td>
</tr>
<tr>
<td>Delayed treatment infliximab</td>
<td>NA</td>
<td>1.8 (0.9 – 3.7)</td>
</tr>
</tbody>
</table>

*Model including treatment timing.
DAS, disease activity score; SE, shared epitope.

analyses for the delayed and initial treatment groups separately showed similar effect sizes, with the exception of smoking (lower HR) and SE (higher HR) in the delayed treatment group (Table 2). The multivariable analyses yielded a model with smoking, SE, and treatment duration, adjusted for treatment timing. Treatment duration was dichotomised with 18 months (fourth quartile) as the cut-off value. The possible interaction between smoking and SE could not be assessed due to small numbers. Smoking (HR 2.1, 95% CI 1.1 to 4.2), treatment duration of 18 months or longer (HR 2.4, 1.1 to 5.4) and the presence of SE (HR 3.7, 1.3 to 10.6) were independently associated with the reintroduction of infliximab (Table 3). Infliximab-free survival was investigated based on the number of predictors present (Figure 3). Of the 18% of patients who had no predictors present, 94% did not need infliximab re-introduction. Of the 40% who had one predictor present, 42% needed infliximab re-introduction, compared with 67% of the patients with two or more risk factors. Because SE is rarely known in clinical practice and SE and anti-citrullinated protein antibody (ACPA) status are highly correlated, we repeated the analyses using ACPA instead of SE. ACPA was not an independent predictor in the original model, nor after omitting smoking. However, of the 18 patients who were non-smokers, had short treatment duration and were ACPA negative, only two (11%) needed infliximab re-introduction (Figure 3D).
Chapter 8 Discontinuation of infliximab and potential predictors of persistent low disease activity

DISCUSSION

In the BeSt study, 45% of patients treated with infliximab were able to discontinue infliximab. Eighty per cent of these patients could stop for at least 1 year, and 52% did not restart during a median follow-up of 7.2 years. In the year after infliximab cessation, significant joint damage progression was rare, regardless of disease flare. Retreatment with infliximab was successful in 84%. Smoking, SE and long infliximab treatment duration (≥18 months) were independent predictors of the re-introduction of infliximab.

Our results are in line with previous reports, although there are differences in patient characteristics, requirements to discontinue or restart TNF blockers and the duration of follow-up. Quinn, et al.11 were the first to report on the successful cessation of a TNF blocker (infliximab), in seven of 10 patients with early RA, regardless of disease activity (which in general was low). Brocq, et al.3 reported on 21 patients with advanced RA who were in remission after delayed treatment with a TNF blocker (six as monotherapy). Five patients successfully stopped the TNF blocker for 12 months. The 16 who flared regained remission after retreatment. Saleem, et al.6 reported a 40% overall success rate in 2 years in 47 patients who had achieved remission and discontinued TNF blockers. Remission was maintained in 60% of patients who had the TNF blocker as initial treatment, compared with three of 20 patients who had had delayed treatment (10 had failed on a previous TNF blocker). The Remission Induction by Remicade in RA (RRR) study by Tanaka, et al.4 has a comparable sample size to ours, and infliximab was also discontinued if a DAS of 2.4 or less was repeatedly achieved. The rate of successful discontinuation of infliximab in 1 year was 55%, compared with 80% in 1 year in the BeSt study. This may be due to a high percentage of BeSt patients who had received infliximab as initial treatment, whereas in the RRR study, all patients received infliximab after failure on various systemic DMARDs. The differences in patient characteristics and follow-up duration may also explain why Tanaka, et al.4 found remission at cessation to be predictive of maintaining a DAS of 2.4 or less, whereas we did not.

The percentage of infusion reactions after retreatment was not increased when compared with infusion reactions during initial treatment in group 4 of the BeSt study, so the hypothesis of Takeuchi, et al.13 of an increased risk of infusion reactions after the re-introduction of infliximab was not confirmed. This might be explained by the design of the BeSt protocol: methotrexate is continued after the cessation of infliximab until sustained remission is achieved on the maintenance dose, and in patients in drug-free remission who flare, first methotrexate is re-introduced and increased before infliximab can be restarted. The presence of antibodies to infliximab was not tested. The rate of serious infections was higher after the re-introduction of infliximab compared with the difference between infection rates during cessation and after retreatment may be the result of physicians choosing intravenous over oral antibiotics in patients using a TNF blocker, longer exposure to infliximab or of longer and more active disease duration. The difference in serious infections between first time infliximab users and restarters could reflect patient selection, because restarters had longer symptom duration and possibly more severe RA, which is associated with a higher infection risk.14,15 To our knowledge, the inverse association between smoking and SE and successful infliximab cessation has not previously been reported. Both characteristics are associated with more severe disease.16-18 Smoking, but not SE, might be associated with poor response to TNF blockers.16-18 Smoking and SE are associated with increased ACPA levels,19 but neither our analysis nor the analysis by Saleem, et al.6 showed a strong association between ACPA and successful cessation, although this may be due to relatively small numbers. For daily practice this is disappointing, because it is not current routine to test for SE. Our analyses did show that of the non-smoking, ACPA-negative patients with short infliximab treatment duration, only 11% needed to restart infliximab.

In the BeSt study, the tapering and cessation of infliximab was DAS steered. Therefore, the association between shorter infliximab treatment duration and continued DAS of 2.4 or less after cessation correlated with the time to achieve a DAS of 2.4 or less for 6 months consecutively while on infliximab. Previously, we reported that patients from the BeSt study who received infliximab as initial treatment were more likely to achieve a DAS of 2.4 or less and discontinue infliximab than patients from the delayed treatment group.20 In the current analysis, an association was found between successful cessation and initial treatment. As patients in groups 1–3 only started methotrexate plus infliximab after failing on three treatment steps, they had longer symptom durations at the time of infliximab cessation, and probably more difficult-to-treat RA than the unselected patients who started with initial methotrexate plus infliximab. The differences in disease characteristics at baseline between the initial and delayed treatment groups corroborate this (table 1). Despite these differences, we combined patients from both groups for the analysis, because we set out to find predictors of successful cessation irrespective of treatment timing, and to gain power. In separate analyses for the two groups, we found similar effect sizes, with the exception of smoking in the delayed treatment group, possibly due to small numbers and a higher proportion of smokers in this group. Previously, we compared the response to infliximab in both treatment groups using propensity scores to adjust for the differences at baseline. As the current subanalysis compares selected patients from the two treatment groups who discontinued infliximab because of a sustained DAS of 2.4 or less, this method cannot be applied. The association between treatment timing and successful cessation was also described by Saleem, et al.6 but that study had comparable limitations. The observed association is thus affected by patient selection based on earlier failure on at least three non-biological DMARD treatment steps and the initiation of infliximab after a ‘delay’ of on average 14 months. Of course in daily practice, in which TNF blockers are currently reserved for patients who fail on non-biological DMARD, one must assume that similar selection processes are at work.

A second limitation of this subanalysis is that for 16/104 patients, the SE status was not known. We included SE in the multivariable model because of the strong association with successful cessation. This resulted in the exclusion of the patients with missing SE data.
In conclusion, infliximab can be successfully stopped for at least 1 year in 80% of patients. Joint damage does not increase in this year, regardless of flare. After a median period of 7.2 years, 52% had not restarted infliximab. Even temporary cessation can benefit both the individual patient and, given the high costs of TNF blockers, society as a whole. Non-smoking, SE-negative or ACPA-negative patients who needed less than 18 months of infliximab treatment very rarely have to restart infliximab due to an increase of the DAS to over 2.4. However, not all of those who have to restart infliximab regain a DAS of 2.4 or less, and restarting infliximab carries a (small) risk of (mild) infusion reactions. We therefore recommend that in particular for patients with one or more of the above-mentioned risk factors, infliximab discontinuation has to be carefully considered on an individual basis.

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Discontinuing treatment in patients with rheumatoid arthritis in sustained clinical remission

Exploratory analyses from the BeSt study

N.B. Klarenbeek, S.M. van der Kooij, M. Güler-Yüksel, J.H.L.M. van Groenendael, K.H. Han, P.J.S.M. Kerstens, T.W.J. Huizinga, B.A.C. Dijkmans and C.F. Allaart

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Chapter 9 Discontinuing treatment in patients in sustained clinical remission

INTRODUCTION

As a result of the increasing percentage of patients achieving remission with the introduction of early, intensive goal-steered therapy, more often the dilemma is whether a patient with rheumatoid arthritis (RA) in prolonged remission could discontinue disease-modifying antirheumatic drugs (DMARDs) or whether treatment should be continued. Stopping DMARDs while keeping remission would be beneficial with respect to adverse events and costs. On the other hand, discontinuation of DMARDs could contribute to a relapse of disease with potential harmful consequences.

Historically, the question whether DMARD therapy can be discontinued has often been asked. Several small studies from the 1970s/1980s assessed the need for long-term DMARD maintenance therapy in patients treated according to the pyramid ‘go low go slow’ approach. These studies reported high relapse rates after discontinuation of DMARDs (range 58%-100%). Later, ten Wolde, et al. performed a randomised clinical trial in 285 patients with long-standing inactive RA and reported flare rates of 38% in the placebo (discontinuation) group versus 22% in the group continuing DMARD therapy. Data on withdrawal of DMARDs in patients with established disease have recently been summarised in a meta-analysis.

Since the approach of RA treatment has shifted towards early intensive goal-steered treatment, the discontinuation of DMARDs has rarely been studied. There are few data on the safety of withdrawing DMARDs, the chance of flares and the response to reintroduction of DMARDs. It is unclear whether a flare after a drug-free remission episode can be predicted. With prediction subgroups of patients might be identified in which medication can be safely withdrawn versus other subgroups in whom treatment should be continued.

The protocol of the BeSt study, a randomised clinical trial in recent-onset RA, allowed discontinuation of DMARDs in patients in prolonged remission under strict control of disease activity. The objectives of this analysis were: (1) to assess the flare rate in patients in drug-free remission; (2) to describe the severity of relapse; (3) to identify predictors for relapse; and (4) to assess the response to reintroduction of DMARDs.

METHODS

Study design and patients

Five-year data of the BeSt study were used. Details of the design have been described elsewhere. In summary, 508 patients with recent-onset active RA according to the 1987 RA classification criteria (disease duration <2 years) were randomised into four treatment strategies: sequential monotherapy (n=126), step-up combination therapy (n=121), initial combination therapy with prednisone (n=133), and initial combination therapy with methotrexate and the tumour necrosis factor α inhibitor infliximab (MTX+IFX, n=128). Treatment was adjusted based on 3-monthly disease activity score (DAS) measurements (Disease Activity Score 44 joints, DAS44), aiming at DAS ≤2.4. If DAS was >2.4 the next...
Discontinuation of DMARD therapy

Remission was defined as a DAS <1.6. Two years after inclusion, the protocol allowed tapering and discontinuation of the last DMARD if patients fulfilled the following conditions: (1) DMARDs in maintenance dose according to the protocol (2) clinical remission (defined as DAS <1.6) for ≥6 months.

For MTX monotherapy, sulphasalazine (SSA) monotherapy, leflunomide and intramuscular gold, the maintenance doses were 10 mg/week, 2000 mg/day, 10 mg every other day and 50 mg every other week, respectively. All combinations were first tapered to MTX monotherapy which was then tapered to 10 mg/week, with the exception of the COBRA combination (MTX, SSA, prednisone) which was tapered to SSA 2000 mg/day as maintenance dose, and the combination azathioprine and prednisolone which was tapered to azathioprine 2 mg/kg/day.

Discontinuation of the last DMARD occurred by tapering MTX with 2.5 mg/4 weeks and SSA with 500 mg/4 weeks; maintenance doses leflunomide, gold and azathioprine were simply discontinued.

Restart of DMARD therapy

If the DAS was ≥1.6, the last tapered DMARD was immediately restarted in maintenance dose and could not be discontinued twice. Patients who remained drug-free until year 5 will be referred to as ‘sustained drug-free remission patients (SDFR)’ whereas patients who restarted before 5 years will be called ‘restarters’.

Statistical analysis

The software program SPSS version 17.0 was used for all statistical analyses. Among the patients who achieved drug-free remission, variables associated with restarting treatment were identified by univariable logistic regression using characteristics from baseline and from the last visit before tapering the last DMARD to 0. A multivariable logistic regression with univariable logistic determinants (p<0.10) was used to identify independent predictors for restart using a backward selection procedure (p<0.05). Subsequently, the multivariable predictors from the backward procedure were entered in a new logistic regression model. Variables that were not associated with restarting treatment in the univariable logistic regression were then added one by one to assess whether they had additional predictive value.

RESULTS

After 5 years 115/508 (23%) patients achieved drug-free remission with no significant differences between the groups (p=0.20, table 1). Of these, 53 (46%) restarted treatment after a median (IQR) period of 5 (2–16) months. Fifty-nine (51%) remained in drug-free treatment of the protocol was taken. If DAS was ≤2.4 for 26 months, treatment was tapered to the maintenance dose. For details on treatment steps per arm see figure 1 in chapter 4.

restart of DMARD therapy

For each treatment group, the medication step at which the drug-free remission was reached is shown separately for the sustained drug-free remission patients, restarters and patients lost to follow up. Before the protocol allowed discontinuation of the last DMARD patients had to taper their medication to DMARD monotherapy in a maintenance dose. If subsequently DAS fell to <1.6 for 26 months, the last DMARD could be tapered/discontinued. Details on tapering and discontinuation are shown below.

1. First MTX was tapered to 10 mg/week if DAS ≤2.4 during 26 months. Subsequently, MTX was tapered to 0 if DAS <1.6 during 26 months on MTX 10 mg/week.
2. SSA was tapered to 0 if DAS <1.6 during 24 months on SSA 2000 mg/day.
3. First leflunomide was tapered to 10 mg every other day if DAS ≤2.4 during 26 months on leflunomide 10 mg every other day.
4. First IFX was discontinued and MTX was tapered to 10 mg/week if DAS ≤2.4 during 26 months on MTX 10 mg/week.
5. First, the step-up combination was tapered to MTX monotherapy and then to MTX 10 mg/week if DAS ≤2.4 during 26 months. Subsequently, MTX was tapered to 0 if DAS <1.6 during 26 months on MTX 10 mg/week.
6. First prednisolone and CZA were tapered to 0 if DAS ≤2.4 during 26 months. Subsequently, SSA was tapered to 0 if DAS <1.6 during 26 months on SSA 2000 mg/day.
7. First prednisolone and CZA were tapered to 0 if DAS ≤2.4 during 26 months. Subsequently, MTX was tapered to 0 if DAS <1.6 during 26 months on MTX 10 mg/week.
8. One patient tapered to MTX 10 mg/week due to SSA toxicity.

CSA, cyclosporin A; DMARD, disease-modifying antirheumatic drug; HCQ, hydroxychloroquine; IFX, infliximab; MTX, monotherapy; pred, prednisolone; SSA, sulphasalazine.
remission with a median (IQR) duration of 23 (15–25 months) at 5 years, and 3 (3%) were lost to follow-up. Details of the treatment steps at which drug-free remission was reached are given in table 2.

In the restarters, mean (SD) DAS increased from 1.13 (0.73) at remission before tapering to 2.18 (0.65) at restart, reflecting an increase in all four components of DAS: median (IQR) erythrocyte sedimentation rate (ESR) increased from 7 (5–14) to 19 (7–28), swollen joint count from 0 (0–6) to 2.5 (0–4), Ritchie Articular Index (RAI) from 0 (0–0) to 3 (0–6), and visual analogue scale (VAS) global health from 15 (2–22) to 28 (15–55). In 38/53 of patients (72%) the highest disease activity during the flare was ≤2.4 (low disease activity), in 12/53 (23%) between 2.4–3.7 (moderate disease activity) and in 3/53 (6%) it was >3.7 (high disease activity).

The presence of anti-cyclic citrullinated peptide (anti-CCP), rheumatoid factor, lower VAS global health and lower health assessment questionnaire (HAQ) at baseline were univariably associated with restarting treatment (table 4). Furthermore, baseline Sharp-van der Heijde (SHS) tended to be higher in those who restarted treatment than in SDFR patients (ns). None of the characteristics at the time of remission were associated with restarting treatment. In the multivariable analysis, the presence of anti-CCP was the strongest independent predictor for restart, followed by a higher mean DAS until remission, lower baseline HAQ and SSA as last DMARD (table 4). Both restarters and SDFR patients had good functional ability during their remission (table 3), comparable to HAQ scores of the general population (age- and sex matched: median [IQR] HAQ 0.20 [0.15–0.34] and 0.18 [0.10–0.49] for restarters versus SDFR, respectively).

Of the 53 restarters, 25 (47%) again achieved clinical remission within 3 months after restarting treatment with the last used DMARD in maintenance dose and another 14 (26%) within 6 months. Eleven patients (21%) achieved a DAS ≤2.4, one patient (2%) did not achieve a DAS ≤2.4 and two patients (4%) were lost to follow-up. The large majority of patients did not show joint damage progression in the first year after discontinuation of DMARDs, with a median (IQR) SHS progression of 0 (0–1) units in the restarters during the year of DAS increase compared with 0 (0–0) in the SDFR patients in the first year completely drug-free (p=0.44, Mann-Whitney-U test, figure 1).

**Table 3** Univariable analysis: potential variables associated with a flare during a drug-free remission period

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Restarters (n=53)</th>
<th>Sustained drug-free remission (n=59)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>50 (11)</td>
<td>50 (13)</td>
<td>1.01 (0.99–1.04)</td>
</tr>
<tr>
<td>Female gender, n (%)</td>
<td>30 (57)</td>
<td>35 (59)</td>
<td>0.69 (0.49–1.02)</td>
</tr>
<tr>
<td>Erosive yes, %</td>
<td>24 (45)</td>
<td>32 (54)</td>
<td>2.0 (0.95–4.4)</td>
</tr>
<tr>
<td>Anti-CCP positive, %*</td>
<td>37 (70)</td>
<td>18 (30)</td>
<td>5.3 (2.4–11.8)*</td>
</tr>
<tr>
<td>RF positive, %*</td>
<td>37 (70)</td>
<td>26 (44)</td>
<td>2.9 (1.3–6.4)*</td>
</tr>
<tr>
<td>Symptom duration (wks), median (IQR)</td>
<td>24 (13–56)</td>
<td>20 (11–40)</td>
<td>1.00 (0.99–1.02)</td>
</tr>
<tr>
<td>HAQ, mean (SD)</td>
<td>4.7 (1.5–7.0)</td>
<td>1.5 (0–6.0)</td>
<td>1.04 (0.99–1.09)</td>
</tr>
<tr>
<td>DAS44, mean (SD)</td>
<td>2.18 (0.65)</td>
<td>1.01 (0.73–1.40)</td>
<td></td>
</tr>
<tr>
<td>SHS, median (IQR)</td>
<td>2.5 (1.0–7.0)</td>
<td>1.5 (0–6.0)</td>
<td>1.03 (0.98–1.08)</td>
</tr>
<tr>
<td>ESR, median (IQR)</td>
<td>7 (5–11)</td>
<td>6 (4–13)</td>
<td>0.99 (0.86–1.10)</td>
</tr>
<tr>
<td>CRP, median (IQR)</td>
<td>5 (2–10)</td>
<td>3 (2–7)</td>
<td>1.02 (0.85–1.20)</td>
</tr>
<tr>
<td>VAS global health, mean (SD)</td>
<td>15 (7–20)</td>
<td>15 (4–20)</td>
<td>1.02 (0.98–1.05)</td>
</tr>
<tr>
<td>Baseline characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline HAQ</td>
<td>0.41</td>
<td>0.19</td>
<td>0.88</td>
</tr>
<tr>
<td>Weighted mean DAS44 until remission</td>
<td>4.7</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>Anti-CCP positive</td>
<td>7.5</td>
<td>2.9–10.4</td>
<td></td>
</tr>
<tr>
<td>Weighted mean DAS44 until remission</td>
<td>4.7</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>Baseline HAQ</td>
<td>0.81</td>
<td>0.39–1.86</td>
<td></td>
</tr>
<tr>
<td>Last DMARD MTX</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>SSA</td>
<td>3.5</td>
<td>1.5–6.2</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Last DMARD MTX</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
</tr>
</tbody>
</table>

* | anti-CCP, anti-cyclic citrullinated peptide; DAS44, disease activity score (44 joints); DMARD, disease modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire; IQR, interquartile range; MTX, methotrexate; n, number of patients; NA, not applicable due to low patient numbers; RAI, Ritchie Articular Index; RF, rheumatoid factor; SHS, Sharp-van der Heijde score; SJC44, swollen joint count 44 joints; SSA, sulphasalazine; VAS, visual analogue scale (mm).
DISCUSSION

We implemented discontinuation of DMARDs early in the course of the disease in patients with RA in clinical remission, treated according to an early, aggressive and dynamic treatment approach. Twenty-three percent of patients could discontinue their DMARDs because of remission during ≥6 months: 51% of them remained in drug-free remission (median 23 months) and 46% restarted treatment. The majority of these restarters again achieved clinical remission within 3–6 months after restarting DMARDs without suffering joint damage progression. Earlier reported relapse rates were comparable or higher (38–100%) than the 46% relapse rate in our study. The largest well-designed study by ten Wolde et al. in patients with established RA showed a relapse rate in the same range as the rate we found in our early RA cohort (38% versus 46%). Direct comparison of these relapse rates is difficult owing to different definitions of relapse/remission and differences in patient populations. In the older studies, the majority of patients had long standing disease with significant joint damage and poor functional ability. We report discontinuation of DMARDs early in the disease course with the key advantage that patients in drug-free remission had limited joint damage and enjoyed a functional ability comparable to an age- and sex-matched healthy reference population.

Tanaka et al. recently published the RRR study on discontinuation of infliximab in patients with RA after attaining low disease activity. As in our study, medication was withdrawn and reintroduced at a predefined cut-off and the occurrence of a flare was registered. This study differs from the BeSt study in several ways. First, in the RRR study, infliximab was discontinued while methotrexate was continued whereas, in the BeSt study, all antirheumatic treatment was withdrawn. Second, in the RRR study, infliximab was discontinued and reintroduced at the low disease activity cut-off point. No clinical remission was required. Furthermore, the disease duration at inclusion was higher in the RRR study (5.9 versus 0.4 years). Despite these differences in study design, the observed chance of a flare was remarkably comparable (45% versus 46%) and, as we found, the majority of patients responded well to reintroduction of treatment after a relapse.

The presence of CCP2 antibodies is one of the strongest known predictors for a worse disease course in RA. In line with this, anti-CCP positive patients have a lower chance of achieving drug-free remission. In addition, we found that among the patients achieving drug-free remission, the presence of anti-CCP was the strongest predictor for the occurrence of a flare. Nevertheless, 30% of the patients in sustained drug-free remission are anti-CCP positive, indicating that, even in anti-CCP positive patients, successful drug-free remission is possible.

Surprisingly, low HAQ at baseline was predictive for restarting treatment in the univariable and the multivariable analysis. The univariable results of VAS general health pointed in the same direction. This suggests that if patients are able to improve more in HAQ – that is, if patients have gained more (mean HAQ improvement 1.14 versus 0.83 in SDFR vs restarters) – they have a higher chance of retaining remission after discontinuation of drugs. Patients who discontinued MTX maintenance therapy had a higher chance of retaining remission than patients who discontinued SSA. Although the patient numbers are low, these results may suggest that SSA is less potent in inducing sustained remission after discontinuation than MTX. Additional research is needed to confirm this finding.

We hypothesised that patients with a DAS just below the cut-off score of 1.6 might have a higher chance of relapse than patients with a lower DAS. We therefore assessed whether the level of inflammation at the time of remission, as measured with the DAS and its components was predictive for a flare. There appeared to be no association between inflammation measures and the risk of flare, indicating that the ‘depth’ of the DAS remission is not useful in predicting whether the remission will be maintained after discontinuation of DMARDs. ‘Deeper’ remission is not ‘true’ remission in that sense.

During the relapse the duration and severity of a higher level of disease activity seems limited. DMARDs in a low maintenance dose were restarted immediately if DAS rose to ≥1.6 and the large majority again achieved clinical remission within 3–6 months. During the flare the DAS increased to a low disease activity level in 72% of patients; few experienced high disease activity during the flare. The temporarily higher DAS level might have contributed to the slightly higher (non-significant) joint damage progression in the restarters than in the SDFR patients. Another explanation could be that the restarters had less favourable characteristics than the SDFR patients, including a higher per-
Chapter 9 Discontinuing treatment in patients in sustained clinical remission

centage of anti-CCP positive patients, leading to a higher risk of progression. This is supported by the observation that, before discontinuing DMARDs, restarters already had more joint damage than patients retaining remission (median SHS 5.0 vs 1.5). Since DMARDs were stopped in all patients in prolonged remission, it is unknown what the flare rate would have been if treatment had been continued. Ten Wolde, et al found that, in patients who continued therapy, the flare rate was also considerable (22%) but significantly lower than in patients discontinuing treatment (38%). Being aware of the differences in patient population, these findings suggest that part of the flares we observed could have happened even if DMARDs were continued.

In summary, in 23% of patients with recent-onset RA, DMARDs could be discontinued because of prolonged clinical remission. Based on strict criteria, almost half of them had to restart treatment. The presence of anti-CCP was the strongest predictor for restarting treatment. The large majority of patients who lost remission remained in low disease activity, regained clinical remission shortly after reintroduction of low-dose mono-therapy and showed no joint damage progression in the year of the restart. We therefore propose that, under continued tight control, discontinuation of the last DMARD can be considered in patients in stable clinical remission. The final decision whether or not to withdraw treatment in an individual patient should be made by the physician and patient together, carefully weighing the advantages and disadvantages.

REFERENCES

Clinical synovitis in a particular joint is associated with progression of erosions and joint space narrowing in that same joint, but not in patients initially treated with infliximab.


Ann Rheum Dis 2010; 69: 2107-2113
Chapter 10 Relationship between clinical synovitis and damage progression at joint level

**INTRODUCTION**

In rheumatoid arthritis (RA) it is well-established that inflammation, joint damage and functional limitations are interrelated. Therefore, the treatment of rheumatoid arthritis is aimed at decreasing disease activity as soon as possible in order to restrict limitations in functional ability and to prevent the progression of joint damage. Although the generally accepted concept that inflammation leads to joint damage forms the basis for current treatment approaches, the number of studies assessing this relationship on the individual joint level are limited. There are several earlier studies on the relationship between clinical signs of synovitis and individual joint damage, but in these studies no correction was made for the fact that multiple joints per patient were included in the analyses, incorrectly assuming that these measurements all came from different patients. Because of patient characteristics it is likely that within one patient two joints behave more similar than two joints from two different patients, that is within one patient measurements of multiple joints are considered to be correlated. This within-patient correlation needs to be taken into account. In the two studies that did correct for within-patient correlation, foot joints are either not included or not studied separately. Furthermore, the influence of treatment with conventional disease-modifying antirheumatic drugs (DMARDs), corticosteroids and biologicals on the relationship between clinical signs of synovitis and progression of joint damage in individual joints is unclear. Clinical trials with tumour necrosis factor (TNF)-blocking therapies showed a disconnect between inflammation and joint damage progression in patients treated with methotrexate and TNF inhibitors at patient level. It can be questioned whether this dissociation exists at joint level.

Therefore, the first objective of our study was to examine the relationship between clinical signs of synovitis (swelling and tenderness) and joint damage progression (erosions, joint space narrowing [JSN], total Sharp-van der Heijde score [SHS]) in the individual joints of the hands and feet of patients with RA. The second aim was to assess the influence of different types of treatment on these relationships.

**METHODS**

The first year follow-up data from the randomised, single-blind Behandel Strategieën (BeSt) study were used for our analysis. Details of the BeSt study design have been published previously. Briefly, 508 patients with recent-onset RA were randomised into four treatment strategies: sequential monotherapy (group 1, n=126), step-up combination therapy (group 2, n=121), initial combination therapy with prednisone (group 3, n=133) and initial combination therapy with methotrexate (MTX) and the TNF-α inhibitor infliximab (group 4, n=128). Treatment was adjusted based on 3-monthly measurements of disease activity aimed at achieving a disease activity score (DAS) ≤2.4 (ie, the cut-off value for low disease activity).

The study was approved by the Medical Ethics Committees of the participating hospitals, and all patients gave written informed consent. The study was designed by the...
investigators and supported by a government grant from the Dutch College of Health Insurance Companies, with additional funding from Centocor (Horsham, Pennsylvania, USA) and Schering-Plough Ltd. Data collection, trial management, data collection, data analysis and preparation of the manuscript were performed by the authors.

**Patients**

Between March 2000 and August 2002, 508 patients from 20 hospitals in The Netherlands with DMARD-naive RA according to the 1987 American College of Rheumatology criteria, age ≥18 years, disease duration ≤2 years, active disease with ≥6 of 66 swollen joints and ≥6 of 68 tender joints and either an erythrocyte sedimentation rate (ESR) ≥28 mm/h or a global health score of ≥20 mm on a 100 mm visual analogue scale (VAS; 0, best; 100, worst) were included.

**Assessment of radiological damage progression**

Radiographs of the hands and feet of each patient taken at baseline and year 1 were scored in one session per patient in random time sequence using the SHS (range 0 to 448 points) by two independent readers blinded to patient identity and treatment allocation. Mean baseline and 1-year follow-up SHS of the two readers were used. Erosion progression in an individual joint was defined as an increase of >0.5 in erosion score, JSN progression for each joint was defined as an increase in JSN score of >0.5 and SHS progression was defined as an increase in SHS score (JSN + erosions) per joint of >0.5 SHS units.

**Clinical examination**

Clinical joint assessments were performed every 3 months by trained nurses, blinded for treatment allocation. Per joint, swelling was assessed as 0 (absence) or 1 (presence). Joint tenderness was assessed per joint using the Ritchie articular index (RAI) recoded for the current analysis as 0 (absence) or 1 (presence, ie, RAI 1, 2 or 3). In total, five clinical assessments were performed in the first year of the study: one at baseline and four during follow-up. We evaluated whether each joint was never (0 out of 5 assessments), once (1 out of 5 assessments) or twice or more (≥2 out of 5 assessments) swollen and/or tender during year 1.

**Statistical analyses**

Statistical analyses were performed using the software program SPSS version 16.0 (SPSS, Chicago, Illinois, USA). The current analysis included only clinical data from the joints of fingers and toes that were evaluated using the SHS. Generalized Estimating Equations (GEE) analyses were used to study the association between clinical signs of synovitis and joint damage progression at the joint level. The first outcome used in the GEE was erosion progression defined as yes (>0.5 units) or no (≤0.5 units), based on 32 joints per patient (hands: 10 metacarpophalangeal joints [MCPs], 8 proximal interphalangeal joints [IPPs], 2 interphalangeal joints of the thumbs [IPIs]; feet: 10 metatarsal joints [MTPs], 2 interphalangeal joints of the first toes [IPIs]). The second and third outcomes used in the GEE were JSN progression and SHS progression (erosion and/or JSN), respectively, both defined as yes (>0.5 units) or no (≤0.5 units), based on 30 joints per patient (same joints as for erosion progression except IPIs of thumbs as these are not assessed for JSN with the SHS method). The GEE corrects for within-patient correlation. The exchangeable correlation matrix was used in all analyses, assuming an equal correlation between all joints. For all three outcomes, the same covariates were added stepwise to the model in the following order: swelling (ever/never of ≥2 out of 5 assessments) alone, than tenderness (ever/never) alone, than swelling and tenderness together and finally swelling, tenderness and the interaction swelling×tenderness together. All analyses were corrected for the following known predictors for joint damage progression and potential confounders: total SHS baseline, erosions at baseline (>0.5 units yes/no per joint for the outcome erosion progression), JSN at baseline (>0.5 units yes/no per joint for the outcome JSN progression), SHS at baseline (>0.5 units yes/no per joint for the outcome SHS progression), age, gender, baseline body mass index, rheumatoid factor (RF) and anti-cyclic citrullinated peptide (CCP2) status (double positive, RF-positive or CCP2-positive, or double negative), treatment group and baseline ESR. The analyses were repeated for the hands and feet separately to assess whether there was a difference in strength of association. To analyse whether there was a ‘dose-response’ for swelling and tenderness, a GEE with the outcomes erosion progression, JSN progression, and SHS progression with a categorical variable (never, once and ≥2x swollen/tender during year 1) was performed for swelling and tenderness separately, corrected for the variables described above.

To assess whether the association between clinical signs of synovitis and joint damage progression was different for clinical synovitis at baseline (ie, before the start of treatment) compared with clinical synovitis during follow-up assessments (ie, during treatment), swelling and tenderness in each joint were categorised in: (1) never, (2) only at baseline, (3) only at a follow-up assessment (once), (4) only at follow-up assessments (twice or more) and (5) at baseline and during follow-up assessment(s). A GEE model with this categorical variable as determinant was performed for all three joint damage progression outcomes, again corrected for the variables described above.

Finally, a separate GEE analysis was performed for each treatment strategy to study the influence of the treatment strategies on the relationship between clinical signs of synovitis and joint damage progression, corrected for the potential confounders as described above.

**RESULTS**

Baseline characteristics between the four groups were comparable, as previously described. At baseline, patients had active disease, with a mean (SD) DAS of 4.4 (0.9) and a mean (SD) HAQ of 1.4 (0.7). The mean (SD) SHS at baseline was 7.1 (10.2), 3.7% of all joints had erosions (>0.5 units), 53% had JSN (>0.5 units) and 8.1% of all joints had SHS >0.5 units. During year 1, 45% of the 13959 joints used in the analysis were at least once swollen and 59% were at least once tender. During year 1, 2.1% of all joints showed...
erosion progression (295/13959 joints), 1.9% showed JSN progression (251/13084 joints) and 3.6% (477/13084 joints) showed SHS progression.

In total, 3.4%, 3.1% and 5.7% of the joints that were ever swollen and tender during year 1 showed erosion progression, JSN progression and SHS progression, respectively, compared with 1.1%, 0.9% and 1.9% of joints that were never swollen or tender (figure 1 A), indicating that although there was more progression in joints that were swollen or tender, the vast majority of swollen and tender joints did not progress during year 1. However, 30 to 40% of joints with progression of erosion and/or JSN were never recorded as swollen during the 5 assessments during year 1 (figure 1 B). The percentages of joints that were swollen and/or tender during year 1 were similar for joints showing erosion progression, JSN progression or SHS progression. Of the 477 joints with SHS progression >0.5, 87 joints were never recorded as swollen or tender. Of those 87 joints, 23 (26%) had baseline damage, compared to 96 (25%) of the 390 progressive joints with swelling and/or tenderness. Median (IQR) SHS progression in the clinically uninvolved joints with SHS progression was 1.0 (1.0 – 1.6) compared to 1.5 (1.0 – 2.5) in the joints that were at least once recorded as swollen and/or tender (p<0.001; Mann Whitney U test). Joints with JSN at baseline had a higher chance to show JSN progression than erosion progression, whereas among the joints with baseline erosions the chance for erosion and JSN progression was comparable (figure 2).

GEE results

The GEE model showed that a joint that was swollen at least once during year 1 had a higher risk for progression than a joint that was never swollen (table 1: model 1). The same was true for joint tenderness (table 1: model 2). Both swelling and tenderness contributed independently to the increased risk for progression (table 1: model 3), but with lower OR than when added separately. The association was comparably strong for swelling and tenderness and as strong for erosion as well as JSN progression. In all models the potential confounders were added. Independent baseline predictors for joint damage progression in the individual joint, that did not influence the association between swelling and tenderness and damage progression (uncorrected data not shown) were: a higher total SHS at baseline, the presence of baseline damage in the same joint, lower age, a higher ESR, presence of anti-CCP2 and RF and initial mono-therapy (table 1). The interaction term swelling*tenderness was not significantly associated with the outcome erosion progression, JSN progression and SHS progression and was therefore omitted from the analysis. Repeating the GEE analyses in the joints without baseline damage gave comparable results (data not shown).

The association between swelling/tenderness and joint damage progression was stronger in the 18-20 joints scored in the hands than in the 12 joints scored in the feet (table 1: model 3). The GEE model showed that a joint that was swollen at least once during year 1 had a higher risk for progression than a joint that was never swollen (table 1: model 1). The same was true for joint tenderness (table 1: model 2). Both swelling and tenderness contributed independently to the increased risk for progression (table 1: model 3), but with lower OR than when added separately. The association was comparably strong for swelling and tenderness and as strong for erosion as well as JSN progression. In all models the potential confounders were added. Independent baseline predictors for joint damage progression in the individual joint, that did not influence the association between swelling and tenderness and damage progression (uncorrected data not shown) were: a higher total SHS at baseline, the presence of baseline damage in the same joint, lower age, a higher ESR, presence of anti-CCP2 and RF and initial mono-therapy (table 1). The interaction term swelling*tenderness was not significantly associated with the outcome erosion progression, JSN progression and SHS progression and was therefore omitted from the analysis. Repeating the GEE analyses in the joints without baseline damage gave comparable results (data not shown).
### Table 5: GEE results for the four treatment strategies separately. In patients treated with sequential monotherapy (group 1), step-up combination therapy (group 2) or initial combination with prednisone (group 3), swelling and tenderness were significantly related to the outcomes erosion progression, JSN progression and SHS progression.

<table>
<thead>
<tr>
<th></th>
<th>Erosion progression</th>
<th>JSN progression</th>
<th>SHS progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hands: Swollen ever</td>
<td>2.4 (1.4 – 3.8)</td>
<td>1.6 (1.1 – 2.1)</td>
<td>1.5 (1.1 – 2.1)</td>
</tr>
<tr>
<td>Hands: Tender ever</td>
<td>0.9 (0.6 – 1.4)</td>
<td>0.86 (0.80 – 0.93)</td>
<td>2.2* (1.1 – 4.4)</td>
</tr>
<tr>
<td>Feet: Swollen ever</td>
<td>1.4 (0.95 – 2.1)</td>
<td>2.3 (1.4 – 3.7)</td>
<td>1.5 (1.1 – 2.1)</td>
</tr>
<tr>
<td>Feet: Tender ever</td>
<td>1.4 (0.95 – 2.1)</td>
<td>2.3 (1.4 – 3.7)</td>
<td>1.5 (1.1 – 2.1)</td>
</tr>
</tbody>
</table>

All corrected for: total SHS baseline, erosions at baseline yes/no per joint (for outcome erosion progression), JSN at baseline yes/no per joint (for outcome JSN progression), SHS at baseline yes/no per joint (for outcome SHS progression), age, gender, body mass index, rheumatoid factor (RF)/anti-CCP2 status (double positive, RF-positive or CCP2-positive, double negative), treatment group and ESR.

### Table 3: GEE results (OR 95% CI) for the outcomes erosion progression, joint space narrowing progression and Sharp-van der Heijde progression yes/no, for hands and feet separately.

<table>
<thead>
<tr>
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<th>SHS progression</th>
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<td>Swollen ever</td>
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</tbody>
</table>

All corrected for: total SHS baseline, erosions at baseline yes/no per joint (for outcome erosion progression), JSN at baseline yes/no per joint (for outcome JSN progression), SHS at baseline yes/no per joint (for outcome SHS progression), age, gender, body mass index, rheumatoid factor (RF)/anti-CCP2 status (double positive, RF-positive or CCP2-positive, double negative), treatment group and ESR.

### Table 2: Model 1: JSN or erosions at baseline yes/no per joint (for outcome erosion progression), JSN at baseline yes/no per joint (for outcome JSN progression), SHS at baseline yes/no per joint (for outcome SHS progression), age, gender, body mass index, rheumatoid factor (RF)/anti-CCP2 status (double positive, RF-positive or CCP2-positive, double negative), treatment group and ESR.

<table>
<thead>
<tr>
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<td>2.4 (1.4 – 3.8)</td>
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<td>Tender ever</td>
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</table>

All corrected for: total SHS baseline, erosions at baseline yes/no per joint (for outcome erosion progression), JSN at baseline yes/no per joint (for outcome JSN progression), SHS at baseline yes/no per joint (for outcome SHS progression), age, gender, body mass index, rheumatoid factor (RF)/anti-CCP2 status (double positive, RF-positive or CCP2-positive, double negative), treatment group and ESR.

### Table 1: Model 2: JSN or erosions at baseline yes/no per joint (for outcome erosion progression), JSN at baseline yes/no per joint (for outcome JSN progression), SHS at baseline yes/no per joint (for outcome SHS progression), age, gender, body mass index, rheumatoid factor (RF)/anti-CCP2 status (double positive, RF-positive or CCP2-positive, double negative), treatment group and ESR.

<table>
<thead>
<tr>
<th></th>
<th>Erosion progression</th>
<th>JSN progression</th>
<th>SHS progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swollen ever</td>
<td>2.4 (1.4 – 3.8)</td>
<td>1.6 (1.1 – 2.1)</td>
<td>1.5 (1.1 – 2.1)</td>
</tr>
<tr>
<td>Tender ever</td>
<td>0.9 (0.6 – 1.4)</td>
<td>0.86 (0.80 – 0.93)</td>
<td>2.2* (1.1 – 4.4)</td>
</tr>
</tbody>
</table>

All corrected for: total SHS baseline, erosions at baseline yes/no per joint (for outcome erosion progression), JSN at baseline yes/no per joint (for outcome JSN progression), SHS at baseline yes/no per joint (for outcome SHS progression), age, gender, body mass index, rheumatoid factor (RF)/anti-CCP2 status (double positive, RF-positive or CCP2-positive, double negative), treatment group and ESR.
Chapter 10 Relationship between clinical synovitis and damage progression at joint level

We found that clinical signs of synovitis in hands and feet are associated with the development of joint damage progression at the individual joint level. The association is as strong for swelling as for tenderness and similarly strong for the outcomes erosion progression, JSN progression and SHS progression.

We showed a dose-response relationship, indicating that a persistent synovitis, that is, the presence of clinical synovitis during two or more out of five clinical assessments, was associated with a higher risk for progression compared with clinical synovitis at only one assessment. The association is probably even stronger for joints that show signs of inflammation during three to five visits, however, due to a dynamic treatment strategy aiming at low disease activity in the BeSt study, the number of joints with synovitis during more than two visits is limited, and therefore we had insufficient power to assess a stronger dose-response effect. Furthermore, our results suggest that a joint with clinical signs of synovitis despite treatment has a worse prognosis than a joint with clinical synovitis before the start of treatment.

The relationship between clinical signs of synovitis and joint damage progression is stronger in hands than in feet. Although there was a significant association between swelling and tenderness were significantly associated with progression of erosions, JSN and SHS in the hands, we did not find a statistically significant association between joint swelling and JSN progression in the feet, we did not find a statistically significant association between joint swelling and tenderness and erosion progression. This may be due to less accurate joint assessments of the feet, and a fewer number of assessable joints in the hands than in the hands (10 MTPs + 2 IP1s joints vs 18-20 MCPs, PIPs, IP1s joints).

The presence of tenderness might be seen as less specific for local inflammatory activity than the presence of swelling. Our analysis showed, however, that joint tenderness contributes independently of swelling to an increased risk for progression in the individual joint. Therefore, to identify joints at risk for damage progression, separate clinical assessments of swelling and tenderness are warranted, as is required when calculating the DAS. As expected, the association between clinical signs of synovitis and joint damage progression explains only part of the total variability of joint damage progression in patients with RA. The risk for damage progression in an individual joint depends on patient characteristics, local joint circumstances, as well as treatment. Age, the baseline presence of erosions or JSN in the joint, total baseline joint damage, presence of anti-CCP and RF, high ESR, and initial monotherapy were observed to be independent predictors for joint damage progression in the individual joint. In addition, the clinical presence of swelling and tenderness multiplies the absolute risk for progression by its OR.

The presence of tenderness might be seen as less specific for local inflammatory activity than the presence of swelling. Our analysis showed, however, that joint tenderness contributes independently of swelling to an increased risk for progression in the individual joint. Therefore, to identify joints at risk for damage progression, separate clinical assessments of swelling and tenderness are warranted, as is required when calculating the DAS. As expected, the association between clinical signs of synovitis and joint damage progression explains only part of the total variability of joint damage progression in patients with RA. The risk for damage progression in an individual joint depends on patient characteristics, local joint circumstances, as well as treatment. Age, the baseline presence of erosions or JSN in the joint, total baseline joint damage, presence of anti-CCP and RF, high ESR, and initial monotherapy were observed to be independent predictors for joint damage progression in the individual joint. In addition, the clinical presence of swelling and tenderness multiplies the absolute risk for progression by its OR.

Previous data suggested a disconnect between inflammation and joint damage in patients treated with TNF blockers at patient level, that is, even when there is little clinical response, treatment with TNF inhibitors can inhibit the progression of joint damage. This disconnect was present at the individual joint level in patients treated with an initial combination of methotrexate and infliximab as well. The exact pathogenic mechanism of the

**TABLE 4** GEE results (OR (95% CI)) for the outcomes erosion progression, joint space narrowing progression and Sharp-van der Heijde progression yes/no, showing the association between swelling, tenderness and joint damage progression split for baseline and follow-up clinical assessments

<table>
<thead>
<tr>
<th></th>
<th>Erosion progression</th>
<th>JSN progression</th>
<th>SHS progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swollen, ever</td>
<td>3.0 (1.9 – 4.5)</td>
<td>4.5 (2.5 – 8.0)</td>
<td>2.9 (1.9 – 4.3)</td>
</tr>
<tr>
<td>Tender, ever</td>
<td>2.7 (1.6 – 4.6)</td>
<td>2.2 (1.6 – 4.8)</td>
<td>2.5 (1.4 – 4.3)</td>
</tr>
<tr>
<td>Step-up combination therapy</td>
<td>1.6 (0.9 – 2.1)</td>
<td>1.7 (0.9 – 3.1)</td>
<td>1.6 (1.0 – 2.7)</td>
</tr>
<tr>
<td>Tender, ever</td>
<td>2.3 (1.3 – 4.0)</td>
<td>3.1 (1.5 – 6.1)</td>
<td>2.0 (1.3 – 3.3)</td>
</tr>
<tr>
<td>Initial combination with prednisone</td>
<td>3.8 (1.5 – 9.4)</td>
<td>2.8 (1.5 – 5.0)</td>
<td>3.2 (1.7 – 6.3)</td>
</tr>
<tr>
<td>Tender, ever</td>
<td>1.8 (0.7 – 4.6)</td>
<td>2.4 (1.2 – 5.1)</td>
<td>2.1 (1.3 – 3.6)</td>
</tr>
<tr>
<td>Initial combination with infliximab</td>
<td>0.9 (0.4 – 2.0)</td>
<td>1.2 (0.8 – 2.8)</td>
<td>1.2 (0.7 – 2.1)</td>
</tr>
<tr>
<td>Tender, ever</td>
<td>1.4 (0.8 – 2.4)</td>
<td>2.0 (0.8 – 4.9)</td>
<td>2.0 (1.1 – 3.9)</td>
</tr>
</tbody>
</table>

All corrected for: total SHS baseline, erosions at baseline yes/no per joint (for outcome erosion progression), JSN at baseline yes/no per joint (for outcome JSN progression), SHS at baseline yes/no per joint (for outcome SHS progression), age, gender, body mass index, rheumatoid factor (RF)/anti-CCP status (double positive, RF-positive or CCP-positive, double negative), treatment group and erythrocyte sedimentation rate.

CCP, cyclic citrullinated peptide; GEE, generalised estimating equations; JSN, joint space narrowing; SHS, Sharp-van der Heijde score.

**TABLE 5** GEE results (odds ratios (95% confidence intervals)) for the outcomes erosion progression, joint space narrowing progression and Sharp-van der Heijde progression yes/no in the four treatment strategies

<table>
<thead>
<tr>
<th></th>
<th>Erosion progression</th>
<th>JSN progression</th>
<th>SHS progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sequential monotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swollen, ever</td>
<td>1.2 (0.3 – 4.5)</td>
<td>1.2 (0.3 – 4.5)</td>
<td>1.2 (0.3 – 4.5)</td>
</tr>
<tr>
<td>Tender, ever</td>
<td>2.7 (1.4 – 5.3)</td>
<td>2.2 (1.3 – 3.8)</td>
<td>2.5 (1.6 – 4.0)</td>
</tr>
<tr>
<td>Step-up combination therapy</td>
<td>1.6 (0.9 – 2.8)</td>
<td>1.7 (0.9 – 3.1)</td>
<td>1.6 (1.0 – 2.7)</td>
</tr>
<tr>
<td>Tender, ever</td>
<td>2.3 (1.3 – 4.0)</td>
<td>3.1 (1.5 – 6.1)</td>
<td>2.0 (1.3 – 3.3)</td>
</tr>
<tr>
<td>Initial combination with prednisone</td>
<td>3.8 (1.5 – 9.4)</td>
<td>2.8 (1.5 – 5.0)</td>
<td>3.2 (1.7 – 6.3)</td>
</tr>
<tr>
<td>Tender, ever</td>
<td>1.8 (0.7 – 4.6)</td>
<td>2.4 (1.2 – 5.1)</td>
<td>2.1 (1.3 – 3.6)</td>
</tr>
<tr>
<td>Initial combination with infliximab</td>
<td>0.9 (0.4 – 2.0)</td>
<td>1.2 (0.8 – 2.8)</td>
<td>1.2 (0.7 – 2.1)</td>
</tr>
<tr>
<td>Tender, ever</td>
<td>1.4 (0.8 – 2.4)</td>
<td>2.0 (0.8 – 4.9)</td>
<td>2.0 (1.1 – 3.9)</td>
</tr>
</tbody>
</table>

All corrected for: total SHS baseline, erosions at baseline yes/no per joint (for outcome erosion progression), JSN at baseline yes/no per joint (for outcome JSN progression), SHS at baseline yes/no per joint (for outcome SHS progression), age, gender, body mass index, rheumatoid factor (RF)/anti-CCP status (double positive, RF-positive or CCP-positive, double negative), treatment group and erythrocyte sedimentation rate.

CCP, cyclic citrullinated peptide; GEE, generalised estimating equations; JSN, joint space narrowing; SHS, Sharp-van der Heijde score.
dissociation between synovitis and joint damage in patients treated with TNF inhibitors is unclear. Altering of the receptor activator for nuclear factor κB ligand (RANKL)/osteoprotegerin (OPG) ratio by TNF blockade and thereby inhibiting osteoclast activation probably plays a role. 12,13 The disconnect again emphasises the important role of TNFα in the development and progression of joint damage.

A limitation of this study might be that there were no ultrasound or MRI data available, which might have given insight in subclinical synovitis. However, the clinical associations we observed are accurate. With ultrasound or MRI a stronger association between synovitis and progression might be observed. Another drawback might be that the percentage of joints with progression was limited, as a result of the effective treatment approach. In conclusion, swelling and tenderness are independently associated with erosion and JSN progression, but not in patients treated initially with MTX and infliximab combination treatment.

REFERENCES

A comparison between the simplified erosion and narrowing score and the Sharp-van der Heijde score

A post hoc analysis from the BeSt study


*Ann Rheum Dis* 2011; 70: 714-716
The Sharp-van der Heijde method (SHS; range 0-448) is an often used and well-validated method to assess joint damage on x-rays in rheumatoid arthritis (RA). It is a comprehensive method that requires training, making it less feasible for clinical practice. The simplified erosion and narrowing score (SENS; range 0-86) scores the same joints as SHS, but without grading of damage per joint, making it quicker and easier to learn.

In earlier studies, SENS showed good reliability and responsiveness, but these studies either had no restrictions in disease duration or limited patient numbers. We aimed to compare the properties of SENS and SHS in a large group of early, intensively treated RA patients with limited joint damage during 5 years of follow-up in the BeSt (Behandel Strategieën [Treatment Strategies]) study. Details of the study have been described earlier.

Annual radiographs of hands and feet in years 0-5 were scored in one session per patient in random time sequence using SHS by two independent readers blinded for patient identity. Per reader, the SENS was derived from the SHS.

In total, 2595 sets of radiographs were present from 498 patients (mean 5.2 sets per patient). Median (IQR)/mean (SD) SHS and SENS at baseline were 3.0 (0.5-9.5)/7.1 (10.2) and 2.0 (0.5-5.5)/3.8 (4.7), respectively. Mean SHS progression in year 1-5, respectively, was 3.4, 1.5, 1.1, 1.5, 1.6; mean SENS progression was 1.7, 0.6, 0.4, 0.5, 0.6.

The reliability of SENS was comparable to SHS with moderate to high between-reader intra-class correlation coefficients (ICCs). Between-reader ICCs for total SHS and SENS varied between 0.74 and 0.93 for both methods. For progression from baseline, between-reader ICCs varied between 0.90 and 0.95 without differences between the methods and was stable over time.

SENS had lower absolute progression scores than SHS, as expected inherent to the scale. In most patients, positive SHS change scores were accompanied with positive SENS change scores. However, the figures illustrate that in patients with large SHS progression the amount of SENS progression is highly variable.

Percentages with progression ≥1 unit were higher for SHS than for SENS (tables 1 and 2). Sensitivity varied between 69 and 89%, and specificity was high (94-99%). Comparable results were observed for progression ≥ the smallest detectable change. In year 1 (delta 0-1) and 5 (delta 4-5), 11% and 27%, respectively, of patients with SHS progression ≥1 units had no progression with SENS. This implies that in these patients damage progression occurs in already damaged joints but does not coincide with the development of damage in previously unaffected joints, in line with Bruynestein, et al. By disregarding grading of damage, the discriminative capacity of SENS is lower. Since differentiation in clinical trials and for example genetics studies, is often based on a minority of patients with joint damage progression, we believe that for research the benefit of time efficiency does not compensate the lower discriminative power of SENS. In daily practice, it may be an acceptable alternative to the SHS.

A limitation might be that we derived SENS from SHS. For comparing reproducibility of SENS and SHS this study design is not ideal. However, this design is appropriate for comparisons of reproducibility.
### Table 2

<table>
<thead>
<tr>
<th>SDC (δ% of maximum score) *</th>
<th>% progression ≥ SDC</th>
<th>% discordance</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SHS SENS SHS SENS SHS + SENS - SENS -</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>delta 1-0</td>
<td>59 (±3)</td>
<td>28 (±4)</td>
<td>20% (86/439)</td>
<td>14% (12/86)</td>
</tr>
<tr>
<td>delta 2-1</td>
<td>55 (±3)</td>
<td>24 (±4)</td>
<td>9% (37/414)</td>
<td>10% (40/414)</td>
</tr>
<tr>
<td>delta 3-2</td>
<td>44 (±3)</td>
<td>21 (±4)</td>
<td>11% (44/398)</td>
<td>7% (29/398)</td>
</tr>
<tr>
<td>delta 4-3</td>
<td>54 (±3)</td>
<td>25 (±4)</td>
<td>10% (40/394)</td>
<td>8% (32/394)</td>
</tr>
<tr>
<td>delta 5-4</td>
<td>63 (±3)</td>
<td>36 (±4)</td>
<td>9% (31/357)</td>
<td>8% (29/357)</td>
</tr>
</tbody>
</table>

SDC, smallest detectable change; SENS, simplified erosion and narrowing score; SHS, Sharp-van der Heijde score.

Values are percentages (n/n), except for SDC.

*SDC (values in parentheses are percentage of maximum score of SHS and SENS in the study, that is, 236 and 64 for SHS and SENS, respectively)

Comparing responsiveness of SENS and SHS, which was the main focus of our analysis. Furthermore, earlier research showed that the concordance between SENS scored separately versus SENS derived from SHS was high (93.8% complete agreement)².

In summary, SENS is a valuable tool in clinical practice due to its time efficiency. However, we do not recommend SENS for research, because it is less sensitive, and by disregarding grading of damage per joint the discriminative power will be lower.

### References


### Chapter 12

#### Blood pressure changes in recent onset rheumatoid arthritis patients treated with four different treatment strategies

A post hoc analysis from the BeSt trial


*Ann Rheum Dis 2010; 69: 1342-1345*
ABSTRACT

Objective: To evaluate the effect of disease activity and antirheumatic treatment on blood pressure (BP) in patients with recent-onset rheumatoid arthritis (RA).

Methods: 508 patients with RA were randomised to receive (1) sequential monotherapy, (2) step-up combination therapy, (3) initial combination with prednisone or (4) with infliximab. Systolic and diastolic blood pressure (SBP, DBP), disease activity score (DAS) and body mass index (BMI) were evaluated every 3 months. A linear mixed model was used to model SBP and DBP in each treatment group during year 1, adjusting for baseline BP, changes in BMI, DAS and cardiovascular medication.

Results: In all groups, mean SBP and DBP were lower for patients with DAS ≤2.4 than for patients with DAS >2.4. In addition, patients initially treated with infliximab (group 4) had a larger decrease in SBP and DBP over time than patients in groups 1-3. The decrease in BP was also observed in patients treated with infliximab after failure on conventional disease-modifying antirheumatic drugs in groups 1-3. The decrease in BP associated with treatment with infliximab occurred irrespective of the DAS response.

Conclusion: A lower DAS is associated with lower BP. An additional BP decrease was observed in patients treated with infliximab. Further research is needed to confirm the effect of infliximab on BP.

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic inflammatory disease which is associated with a higher prevalence of cardiovascular morbidity and mortality, possibly through effects on blood vessels that resemble the pathophysiology of atherosclerosis. Antirheumatic treatment aims at diminishing disease activity and thereby probably decreases cardiovascular risk. Various antirheumatic drugs may have other favourable and/or unfavourable effects on cardiovascular risk.

Because cardiovascular diseases account for a considerable burden of morbidity and mortality in patients with RA, the effect on cardiovascular risk should be considered when choosing a treatment strategy. Hypertension, a risk factor for developing cardiovascular disease, is highly prevalent in patients with RA. We analysed the relationship between disease activity and blood pressure (BP) and the effect of four different RA treatment strategies on BP during the first two years of treatment.

PATIENTS AND METHODS

The BeSt study is a multicenter randomised clinical trial in disease-modifying antirheumatic drug (DMARD)-naïve patients with active RA (disease duration ≤2 years) comparing four different treatment strategies: sequential monotherapy (group 1, n=126), step-up combination therapy (group 2, n=121), initial combination therapy with prednisone (group 3, n=133) and initial combination therapy with methotrexate and the tumour necrosis factor α (TNFα) inhibitor infliximab (group 4, n=128). Details of the study, including data about antirheumatic treatment in the four treatment arms, have been published previously.

Treatment was adjusted based on 3-monthly disease activity score measurements (DAS44). If a patient had a DAS >2.4, treatment was adjusted according to the pre-defined protocol for each group. If the DAS was ≤2.4 (low disease activity (LDA)) for at least 6 months, medication was tapered to a maintenance dose. Every 3 months, as part of a vital signs check, single measurements of systolic and diastolic blood pressure (SBP and DBP, respectively) were performed by trained nurses, blind to the treatment allocation. BP was measured according to local clinical standards: in 16 centers a sphygmomanometer plus stethoscope was used and in four centers electronic devices were used. For each patient, the measurement method was the same during the study period. BP readings were performed at least one hour before or 4 weeks after, administration of infliximab (infliximab infusions every 8 weeks). Patients were classified into four DAS categories at each 3-monthly visit: remission (DAS <1.6), LDA (DAS ≥1.6 but ≤2.4), moderate disease activity (MDA, DAS >2.4 but ≤3.7) and high disease activity (HDA, DAS >3.7). Patients with a DAS ≤1.6 from 6 to 24 months (one DAS ≥1.6 allowed) were classified as ‘continuous remission’. Patients with a DAS >2.4 from 6 to 24 months, (one DAS >2.4 allowed) were classified as ‘continuous clinical failure’.

The decrease in BP associated with treatment with infliximab occurred irrespective of the DAS response.
Statistical analysis
The SPSS 16.0 software package was used. Baseline characteristics were analysed using one-way analysis of variance, the Kruskal-Wallis test and the chi-square test. Two different linear mixed model (LMM) analyses were performed for SBP and DBP all with the unstructured covariance matrix. The first LMM was performed to compare SBP and DBP among the different DAS-categories based on all nine BP measurements per patient, corrected for age, gender, body mass index (BMI), the use of antihypertensive medication at baseline and the use of non-steroidal anti-inflammatory drugs (NSAIDs)/cyclo-oxygenase-2 inhibitors (COXIBs) at baseline and during follow-up. Then LMM was used to model SBP and DBP during the first year of follow-up because from the protocol it follows that patients who were initially treated with infliximab or prednisone used it for at least 7.5 to 9 months. SBP and DBP at the four follow-up visits of year 1 were used as outcomes, with time (as factor) and baseline SBP or DBP, randomisation, age, gender, NSAID/COXIB use at baseline and during each follow-up visit, antihypertensive drug use at baseline, delta DAS and delta BMI (both for each visit compared with baseline) as fixed effects and a random patient effect.

RESULTS
The baseline characteristics between the four treatment groups were comparable. Mean (SD) DBP (mmHg) at baseline was high to normal in all groups: 138 (20) / 84 (10), 140 (21) / 85 (12), 136 (21) / 85 (12) and 136 (20) / 84 (11) for groups 1-4 respectively. At baseline, mean (SD) DAS was 4.4 (0.9), 34% smoked and mean (SD) BMI was 26 (5) kg/m². Of all patients, 22% had a medical history of cardiovascular disease, comprising mainly hypertension (31%), peripheral vascular disease (26%) and acute coronary syndrome (19%). In groups 1-4, 14%, 17%, 14% and 7% of patients were on anti-hypertensive medication at baseline, whereas 87%, 80%, 89% and 87% used NSAIDs or COXIBs. Detailed baseline characteristics and cardiovascular comedication at baseline are shown in table 1. During the 2 years of the study, 27 patients were lost to follow-up. Mean DAS improved earlier in patients in treatment group 3-4 than in group 1-2. From year 1 onwards, disease activity was comparable and stable in all groups. Patients with LDA (DAS ≤2.4) had, on average, lower SBP and DBP than patients with MDA/HDA (DAS ≥2.4) (LMM, figure 1) also after correction for age, gender, BMI and the use of antihypertensive medication and NSAIDs/COXIBs at baseline and during follow-up. A similar effect was observed for the mean DBP values.

Figure 2 shows the progression of SBP and DBP in the four treatment groups over time. After correction for the change in DAS from baseline, baseline SBP, age, gender, NSAID/COXIB at baseline and during follow-up, antihypertensive drug use at baseline and delta BMI, longitudinal data analysis of the first year (LMM) showed that initial combination treatment with infliximab was associated with a reduction in SBP of 4.8 mmHg compared to sequential monotherapy (p=0.001, 3.0 mmHg compared to step-up combination therapy (p=0.04) and 4.5 mmHg compared to initial combination treatment with prednisone (p=0.002). Patients in group 4 also had lower DBP than patients in the other groups, although this was less pronounced and partly non-significant (table 2). No statistically significant differences were found between the other treatment groups, with the exception of a decrease in DBP of 2.0 in group 3 compared to group 1 (table 2). Study center and the use of leflunomide or ciclosporin did not influence the association between treatment and BP and were therefore omitted from the analysis.

In group 4, 22 patients (17%) were classified as ‘continuous clinical remission’ and 11 (9%) as ‘continuous clinical failure’ on infliximab. A comparable decrease in BP was observed with prednisone (p=0.002). Patients in group 4 also had lower DBP than patients in the other groups, although this was less pronounced and partly non-significant (table 2).
in these patients (SBP -6.8 mmHg, DBP -1.7 mmHg for patients classified as ‘continual clinical remission’ and SBP-4.9 mmHg, DBP -10 mmHg for those classified as ‘continuous clinical failure’). In accordance with the protocol, patients who had a continuous good response on infliximab and those who failed on the highest dose discontinued infliximab. At the end of the 2-year observation period when the average blood pressure appeared to return to the original value, only 18% of patients were still receiving infliximab.

In total, 70 patients in groups 1–3 switched to treatment with methotrexaat and infliximab because of DAS >2.4 on prior treatment steps. In these ‘delayed infliximab patients’, SBP decreased on average 2.2 and 4.7 mmHg after 6 and 12 months, and DBP decreased 1.3 and 3.9 mmHg after 6 and 12 months. These changes are not statistically different from the changes observed in patients initially treated with methotrexaat and infliximab.

**DISCUSSION**

This study shows that, in patients with RA, lower disease activity is associated with lower BP. This may represent part of the mechanism by which antirheumatic treatment can reduce the increased cardiovascular morbidity and mortality in RA. It is thought that systemic inflammation in RA leads to vasoconstriction and hypertension through up-regulation of the angiotensin II type 1 receptor and of endothelin and downregulation of NOx.14 Effective suppression of inflammation may inhibit this process, and, as a consequence, may lower BP.

Intriguingly, we found an additional reduction in SBP (up to almost 5 mmHg) and to a lesser extent (up to almost 3 mmHg) in DBP in patients treated with infliximab. Given that patients with RA are at increased risk for developing cardiovascular disease, such decreases in BP could be beneficial.14,18 In the LMM, initial treatment with infliximab was associated with a reduction in SBP compared with the other strategies and also after correction for the improvement in disease activity. Decreases in SBP and DBP were observed in patients who received infliximab as initial therapy and in those who received infliximab after failing on previous treatments, although the latter had a less pronounced reduction in disease activity. Lower BP was seen in patients who failed on infliximab as well as in those who responded with continuous remission. These results

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**TABLE 2** Linear mixed model results with systolic and diastolic blood pressure from 3, 6, 9, and 12 months as outcome, corrected for baseline SBP, time (as factor), age, gender, use of NSAIDS/COXIBs at baseline, use of NSAIDs/COXIBs during follow-up, use of antihypertensive drugs at baseline, delta DAS, delta BMI, and a random patient effect.

<table>
<thead>
<tr>
<th>Group 1 – 2</th>
<th>Beta</th>
<th>95% CI</th>
<th>Beta</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 – 3</td>
<td>1.82</td>
<td>-1.11 – 4.75</td>
<td>1.28</td>
<td>-0.45 – 2.99</td>
</tr>
<tr>
<td>Group 1 – 4</td>
<td>-0.32</td>
<td>-2.57 – 2.91</td>
<td>2.04</td>
<td>0.35 – 3.73</td>
</tr>
<tr>
<td>Group 2 – 3</td>
<td>1.23</td>
<td>0.68 – 1.98</td>
<td>2.81</td>
<td>1.46 – 4.16</td>
</tr>
<tr>
<td>Group 2 – 4</td>
<td>3.01</td>
<td>0.08 – 5.93</td>
<td>1.54</td>
<td>-0.17 – 3.24</td>
</tr>
<tr>
<td>Group 3 – 4</td>
<td>4.57</td>
<td>1.70 – 7.46</td>
<td>0.77</td>
<td>-0.80 – 2.34</td>
</tr>
</tbody>
</table>

Beta represents differences in blood pressure between the groups; > 0: first treatment group mentioned has higher blood pressure; < 0: first treatment group mentioned has lower blood pressure.
suggest that treatment with infliximab has a drug-specific effect on BP which is independent of the level of inflammation measured by the DAS. After 2 years the benefit of infliximab on SBP seems to disappear, probably due to discontinuation of infliximab in the most patients in accordance with the protocol.

To our knowledge, the effect of TNFα inhibitors on BP has not yet been described. There are, however, observations that anti-TNFα treatment is able to reverse endothelial dysfunction, decrease arterial stiffness, and decrease plasminogen activator inhibitor-1 in patients with RA.

The BeSt study was not designed to analyse BP changes associated with antirheumatic treatment. The single BP measurements, done without a standardised measurement protocol, may have led to inconsistent BP measurements. Although the possibility of bias cannot be excluded, we think it is unlikely since the data collection occurred before the hypothesis was formulated, the nurses who measured BP were blind for treatment allocation and we found that adding the variable study center to the analyses did not change the results. The use of cardiovascular concomitant medication and of NSAIDs and COXIBs could have interfered with the observed differences between the groups, although we tried to correct for this in the analyses. Ideally, our BP data should be combined with observations on the occurrence of cardiovascular adverse events. However, the BeSt study was not designed or powered to detect possible differences in such events and few have occurred within the first 2 years of the trial.

Being aware of these limitations, the decrease in BP in patients treated with methotrexate and infliximab remains an interesting and probably clinically relevant observation that needs further investigation.

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Summary and general discussion
This thesis focuses on treatment strategies and outcome measures in rheumatoid arthritis. In Chapter 1 a general introduction for this thesis is given. Rheumatoid arthritis (RA) is an inflammatory autoimmune disease characterised by synovitis, particularly of small joints of hands and feet, although larger joints can be involved as well. Patients with RA often suffer general complaints like fatigue and morning stiffness and may suffer extra-articular manifestations. RA is associated with severe morbidity and even mortality if not treated properly. The last decades RA has been evolved from a disease where treatment was aimed at symptom relief towards a disease where treatment is aimed at disease control. Hereby, the outlook of patients diagnosed with RA improved dramatically. The early institution of disease-modifying antirheumatic drugs (DMARDs), combination therapy, the availability of drugs specifically targeting the immune system (biologics) and tight-controlled treatment, aiming at minimal disease activity have contributed to this improvement and led to a shift in treatment paradigm. Strategy trials and radiological outcome

Strategy trials
Randomised double-blind clinical trials to investigate the efficacy of treatment usually have a static design with a head-to-head comparison of different (combination of) drug(s) during a mostly limited duration of follow-up. Although this a valuable and indispensable ‘gold standard’ design to compare the efficacy of drugs, the translation to clinical practice can hamper. Treating a chronic disease in clinical practice is a dynamic process, with therapy changes in case of insufficient response (treatment to target), adverse events or other patient- or drugs related factors. Strategy trials have a dynamic design, which more resembles daily practice. Instead of the emphasis on the static comparison of individual drugs, the emphasis lies on the application of the different treatment options in a continuous, dynamic, more individualized and ‘real life’ approach. These dynamic trials play a pivotal role in translating the available evidence from RCTs to clinical practice. Chapter 3 summarises recent strategy trials in the treatment of rheumatoid arthritis. The BeSt study (acronym for ‘Behandel Strategieën’, Dutch for ‘treatment strategies’), which is the base of this thesis, is an example of a strategy trial.

The BeSt study
In the BeSt study, 508 patients with recent-onset rheumatoid arthritis (less than two years) according to the 1987 American College for Rheumatology (ACR) criteria were randomised into four treatment strategies: 1. sequential monotherapy (n=126), 2. step-up combination therapy (n=121), both starting with methotrexate monotherapy, 3. initial combination therapy with a tapered dose of prednisone (n=133), and 4. initial combination therapy with the tumour necrosis factor (TNF) α inhibitor infliximab (n=128). In each strategy, patients were treated according to a stepwise protocol, all aiming at low disease activity. Every 3 months the disease activity score (DAS) was calculated. If the DAS was 2.4 or lower (i.e. low disease activity) treatment was continued and tapered to a maintenance dose after 6 months. If the DAS was above 2.4 the next step of the protocol was taken. In total, 20 hospitals in the south-western part of The Netherlands have participated in the BeSt study.

Primary outcomes were functional ability, 3 monthly measured with the health assessment questionnaire (HAQ) and annual joint damage progression assessed on X-rays of hands, wrists and feet. Secondary outcomes were patient-reported outcomes (quality of life) and clinical remission percentages. Analysis of the first two years of follow-up showed an earlier improvement in disease activity, functional ability and quality of life, earlier clinical remission and less radiological damage progression in the initial combination therapy groups compared to the initial monotherapy groups. Due to continuous measurement of disease activity and changes in treatment if disease activity was too high, from one year onwards, clinical parameters were comparable across all groups and stable during 5 years of follow-up (Chapter 4). After 5 years the initial combination therapy groups showed less joint damage than the initial monotherapy groups. A detailed analysis of joint damage progression showed that after 5 years of follow-up the lower total joint damage progression in the combination therapy arms compared with the monotherapy groups is based on less progression during the first year of treatment, reflecting earlier clinical improvement. In later years annual progression rates were comparable between the monotherapy and combination therapy arms. There were no major differences in toxicity between the four treatment arms.

Setting a treatment goal and its association with clinical and radiological outcome
Abundant evidence showed the association between disease activity measures, functional ability and joint damage progression, providing a rationale for early reduction of disease activity in rheumatoid arthritis with effective treatment strategies. Early in the disease course functional limitations are mainly determined by active inflammation (largely reversible), whereas with increasing disease duration, joint damage adds to functional limitations (largely irreversible). In the BeSt study treatment was aimed at low disease activity (DAS ≤2.4), which was associated with a mean HAQ of 0.8 after 5 years of follow-up irrespective of initial treatment. To analyse the association between disease activity and functional ability in more detail, in Chapter 5 a longitudinal analysis of disease activity and functional ability was performed. By using interaction terms we analysed whether the association between a change in DAS and a change in HAQ was dependent on follow-up duration and absolute DAS-value. We found that a larger decrease in DAS is associated with a larger decrease in HAQ. This association was dependent on the absolute DAS-level but did not change with follow-up duration. According to the model, a DAS decrease from 2.5 to 1.5 will improve HAQ more than a decrease from 3.5 to 2.5, probably because of more residual disease activity. A matrix was constructed to visualise the findings. These data suggest that striving for the lowest possible disease activity is valuable, in early and in longstanding disease.
The original DAS have been criticised for its complicated tender joint count: the Ritchie articular index.\textsuperscript{11} With the RAII 53 joints are scored for tenderness on a graded scale of 0–3 per joint, it uses joint groups of which only the highest tender score per joint counts and the joints differ from the 44 joints assessed for swelling. In chapter 6 we validated three simplified versions of the DAS with simplified tender joint counts to replace the RAII: a variant omitting the grading (DAS 0-1), a variant omitting the grading and the grouping (DAS-TJC53) and a variant omitting the grading and grouping and using only the 44 joints which are assessed with the swollen joint count (DAS-TJC44). We compared these three variants with the original DAS. The correlations between the alternatives and the original DAS is high, and the classification into clinical remission, low disease activity (LDA), moderate disease activity (MDA) and high disease activity (HDA) using the cut-offs of the original DAS was highly comparable. In addition, the percentages of patients with rapid radiological progression (>5 SHS points in 1 year) in the different disease activity levels showed high agreement across the DAS variants. These results indicate that a simplified DAS variant seems a valid alternative to the original DAS. The DAS-TJC44 may be the most practical because it assesses the same joints for swelling and tenderness.

In addition to changing the tender joint counts, in chapter 6 we also evaluated the original DAS and its variants using either a patients’ global assessment of disease activity (PGA) or of general health (GH), both assessed on a visual analogue scale of 0–100 mm. In literature both versions are used, but it was unknown whether these were interchangeable. Although both VAS scores in individual patients could differ considerably, used as part of a composite score the difference is negligible, probably because of the limited weight of this component in the total score. These results suggest that both can be used, confirming the study by Khan, et al.\textsuperscript{12}

After the development of the original DAS, a variety of composite indices to measure disease activity have been published, all with proposed cut-offs for remission, LDA, MDA and HDA. All these composite indices have shown to be related to functionality and joint destruction. No direct comparison of the indices was made so far and no consensus exists on which index should be used. In chapter 7 we compared the classification in disease activity levels of 9 often used composite indices and found considerable variation in the proportion of patients in the subsequent levels across the different indices.\textsuperscript{13-16} CDAI and SDAI classified more patients in low disease activity and less in remission; DAS28 and DAS28 with CRP had a smaller proportion in LDA and more in remission and MDA. However, all indices showed a ‘dose relationship’ with the outcomes functional ability and joint damage progression in a remarkably similar way, raising the question of the clinical relevance of the differences in classification.

In addition to the longitudinal association between DAS and HAQ as analysed in chapter 5, these data suggest the importance of setting a strict treatment goal, ie remission, because remission is associated with the fewest functional limitations and joint damage progression. This is in line with the EULAR recommendations for the treatment of RA and the recommendations of the international ‘Treat to target’ initiative in which clinical remission is recommended as treatment goal.\textsuperscript{17} Unfortunately, a large clinical trial comparing remission versus low disease activity as treatment goal with the outcomes functional capacity, progression of joint damage and quality of life is lacking until now. Such a trial would provide direct evidence for the (possible) gain of using clinical remission as treatment goal compared with the treatment goal low disease activity.

**Remission**

In chapter 7, 13 remission definitions have been compared, including four variants of the 2011 ACR/EULAR remission criteria: clinical practice and clinical trial, with 28/28 as well as 68/66 joint counts.\textsuperscript{18} The most stringent remission definition was ACR/EULAR clinical trial remission with 68/66 joint counts classifying the least patients in remission, followed by the other variants of the 2011 ACR/EULAR remission criteria set. From the composite scores the strictest definitions were SDAI remission and CDAI remission, followed by remission defined with the original DAS and his variants. The DAS28 with BSE or CRP classified most patients in remission. The main question is whether the difference in classification, what might be based on relevant residual disease activity in the less stringent definitions, is associated with worse outcome in daily functioning and the occurrence of joint damage progression. With generalised estimating equation (GEE) analyses we analysed the association between all remission definitions, functional ability (measured with HAQ) and joint damage progression (measured with the Sharp-van der Heijde method) on a continuous and on a dichotomous scale. As expected, remission was associated with better functional ability and less joint damage progression according to all definitions. Although the proportions of patients classified as having clinical remission vary considerably between the different definitions, the absolute predicted HAQ and Sharp-van der Heijde progression showed high accordance, as did the estimated probabilities of HAQ >0.5 and SHS progression ≥3.0 in all indices. Although a direct statistical comparison is lacking, the clinical relevance of the differences in HAQ and SHS progression between the different definitions seems limited. This raises questions about the validity of remission definitions, especially the strict definitions. It suggests that the difference between strict and less strict definitions might not be based on clinical relevant residual disease activity, at least not leading to a significant change in daily functioning and joint damage progression.

Which remission definition should be preferred? Since all definitions perform comparable despite considerable differences in classification, there is no clear answer to this question and the answer will largely be based on personal preferences. The 2011 ACR/EULAR remission criteria have to prove value in future research.

How can existing remission definitions be improved? Clinical remission is associated with radiological remission on the group level; however, on individual patient level all available clinical remission criteria allow some residual disease activity associated with joint damage progression (chapter 7). Therefore, parallel to clinical remission, radiological remission should be part of a remission definition, but finding a proper definition is a challenge. Besides a radiological outcome, an ideal remission definition should include a timeline. Real remission is durable and stable over time.
Discontinuing medication

Targeted treatment with a predefined goal with treatment adjustments until the goal is reached is recommended in RA treatment. However, no recommendations are published on what to do if a treatment target is reached. Should medication be continued or is it possible to taper or even complete discontinue treatment? Discontinuation can be beneficial regarding adverse events and costs but, on the downside, may stimulate a relapse of disease with potential harmful consequences. Is it possible to predict which patients have a high risk for a flare of disease? In the chapters 8 and 9 the discontinuation of infliximab in patients with persistent low disease activity and discontinuation of all drugs in patient in persistent remission has been assessed, respectively.

Discontinuing infliximab in persistent low disease activity

Treatment with a TNF inhibitor combined with methotrexate is effective in the early effective suppression of disease activity and the prevention of joint damage, but is expensive and has a possible risk for adverse events. Therefore, the early discontinuation of TNF blockers might be beneficial. In the BeSt study infliximab was discontinued if patients had low disease activity for at least six months. In chapter 8 the discontinuation of infliximab is studied in more detail, in patients who initially started infliximab (group 4) as well as in patients starting infliximab after failing at least three conventional DMARDs (groups 1 to 3). In total, 45% of patients treated with infliximab were able to discontinue infliximab. Of those 80% were able to stop for at least one year and 48% had to restart infliximab because of a flare of disease during a median follow-up period of 7.2 years. The amount of joint damage in the year after stopping infliximab was limited, irrespective of the occurrence of a flare. Retreatment of infliximab was successful in 84%. Predictors for a flare of disease were smoking, the presence of shared epitope and long infliximab treatment (>18 months). These results are largely in line with the limited number of studies on discontinuing TNF inhibitors, although differences in patient characteristics, study designs and requirements for the discontinuation of TNF blockers differed, harming a direct comparison. Since even temporarily discontinuing TNF inhibitors can be beneficial with regards to costs and adverse events, the cessation of TNF inhibitors should be considered in individual patients with persistent low disease activity with little risk factors for a flare under strict control of disease activity.

Drug-free remission

With the growing percentages of remission with new effective and early treatment, the question whether treatment should be continued or can be discontinued in patients in long term remission becomes more important. Discontinuation of treatment in clinical remission has rarely been studied in modern treatment approaches. From the beginning of the BeSt study remission percentages were higher than expected beforehand in this population with recently diagnosed active RA. After 5 years, 48% of patients were in clinical remission, defined as DAS <1.6, without differences between the treatment arms (chapter 4). Because of the high remission percentages, the BeSt study incorporated discontinuation of treatment in patients in prolonged clinical remission (>6 months) from the third year onwards. The last effective drug was immediately reintroduced in case of losing remission. After 5 years 10-19% of patients were in drug-free remission (completers analysis), for a median duration of 23 months (chapter 4). In chapter 9 drug-free remission is studied in more detail. In total, 23% of all patients achieved drug-free remission during 5 years of follow-up, of whom 51% were still drug free after 5 years follow-up (median 23 months), 46% had to restart treatment because they lost remission, and 3% were lost to follow-up. Predictors for a relapse were the presence of anti-cyclic citrullinated peptide antibodies (anti-CCP), sULSAAZ as last DMARD, low baseline health assessment questionnaire (HAQ) score and high mean DAS until remission. The DAS and its components immediately before discontinuation were not predictive for the occurrence of a flare. After restarting treatment, the majority of patients again achieved clinical remission after 3-6 months. Joint damage progression was slightly higher in the patients who restarted treatment compared to the sustained drug-free remission group. The patients who restarted treatment had an unfavourable risk pattern for joint damage progression: positive anti-CCP and more joint damage at the time of discontinuation. A controlled discontinuation study would be necessary to assess whether the relapses and the small amount of joint damage would have occurred when medication was continued. Such a randomised-controlled stop trial is currently performed in the Netherlands (POEET study), in which TNF inhibitors are discontinued in patients in prolonged clinical remission, while continuing conventional DMARDs like methotrexate. Before the arrival of biologicals, Ten Wolde, et al. performed a double blind placebo-controlled discontinuation study in patients with longstanding disease who were in clinical remission in which all antirheumatic medication was discontinued. There, discontinuation of treatment led to more disease flares. Despite large differences in patient populations, these data suggest that the relapse rate is probably higher than it would have been if medication was continued. On the other hand, the data also suggest that a considerable part of patients would have relapsed irrespective of continuing or discontinuing medication. Taking these factors into consideration, discontinuation of medication can be considered in patients in prolonged remission. Discontinuation should be performed under strict control of disease activity and as a shared decision between patient and the rheumatologist, carefully weighing benefits and risks.

Clinical synovitis versus progression of joint damage

The interrelationship between disease activity, functional ability and progression of joint damage is well-established and forms the basis of current treatment approaches. Although generally accepted, limited studies assessed the association between clinical signs of synovitis (tenderness, swelling) and progression of joint damage on the individual joint level in a methodological correct manner. In chapter 10, clinical assessments of tender and swollen joints during year 1 in patients of the BeSt study were related
Chapter 13 Summary and general discussion

The dose-response relationship was found in the first follow-up year, underlining the importance of early effective targeted treatment. The association was found to be stronger in hands than in feet, probably because of more difficult joint assessments in the feet. Although there is a clear relationship, clinical signs of synovitis explain only a part of the total variability leading to the progression of joint damage. Several known and unknown factors determine the risk for joint progression in the individual joint: patient characteristics, local joint circumstances and treatment. Besides swelling and tenderness, known predictors for joint damage progression like auto-antibodies (anti-CCP and rheumatoid factor), acute phase reactants, age, total baseline joint damage, baseline damage per joint, were also found to be related to progression of erosions and joint space narrowing in the individual joint. Beyond these factors, the presence of swelling and tenderness increases the risk for progression by its odds ratio.

We found that the treatment strategy interacts with the association between clinical signs of synovitis and joint damage progression, both with tenderness and swelling. Analysis per treatment strategy showed that in patients treated with initial combination therapy including infliximab there was no statistically significant association between signs of synovitis and joint damage progression, this in contrast to the findings in the other three treatment arms. These results confirm at joint level a disconnect between clinical inflammation and joint damage progression that has been shown earlier on patient level30 and underline the importance of the pro-inflammatory cytokine tumour necrosis factor (TNF) alpha in the pathophysiology of joint damage.

Assessing progression of joint damage in clinical practice

Regular assessments of joint damage progression should be part of clinical practice when treatment is evaluated. Irrespective of clinical parameters, treatment change should be considered if patients show joint damage progression on x-rays, which on the long term may lead to functional limitations. Joint damage progression without clinical symptoms might be the only hint of subclinical inflammation indicating that treatment is insufficient. Ideally, joint damage progression should be assessed using a structured scoring method. Used methods as the Sharp-van der Heijde method and Larsen score are comprehensive, time-consuming and require training which hamper the use in clinical practice. In chapter 11 a comparison between the comprehensive, well-validated Sharp van der Heijde method and the simplified erosion and narrowing score (SENS) is made.

SENS ignores grading of damage per joint, is around three times faster than the Sharp-van der Heijde method and is quicker and easier to learn. The results showed that SENS is a valuable and structured method for assessing joint damage in clinical practice due to its time efficacy. However, SENS is not recommended in research because the method is less sensitive and because grading of damage is disregarded, the discriminative power will be lower.

Cardiovascular disease

The (patho)physiological phenomenon inflammation is thought to play a role in a variety of diseases of which atherosclerosis is an example.31 Rheumatoid arthritis carries a higher risk for cardiovascular diseases, which is suggested to be comparable to the effect of having diabetes mellitus.32 Besides a higher prevalence of traditional risk factor in RA, shared inflammatory pathways between RA and atherosclerosis probably contributes to the increased risk. Because of this increased risk, attendance should be paid to traditional risk factors including life style changes and optimal treatment of hypertension, hypercholesterolemia and diabetes mellitus. Additionally, attention should be paid to the role of treatment of RA in relation to cardiovascular disease and its risk factors. Chapter 12 shows an association between disease activity level and blood pressure. Although small, the association was present for systolic and diastolic blood pressure suggesting that a lower level of inflammatory activity is associated with a more favourable cardiovascular risk pattern. Furthermore, we observed a decrease in systolic and diastolic blood pressure in patients treated with the combination methotrexate and the TNFα inhibitor infliximab, in the other groups no decrease was observed. These results should be interpreted with caution because the BeSt study was not developed to compare blood pressure and observations were based on single blood pressure measurements without a measurement protocol. Nevertheless, in the light of the high burden of cardiovascular disease in rheumatoid arthritis patients this might be a clinical relevant observation.

Early start?

The BeSt study illustrates that with effective treatment early in the disease course, a significant improvement in clinical parameters and limited joint damage progression is realistic in a group of patients with active rheumatoid arthritis. At baseline, all patients fulfilled the 1987 classification criteria for rheumatoid arthritis. The process of developing rheumatoid arthritis can be seen on a timeline from an unknown pathophysiological event at the beginning, auto-antibody responses, towards subclinical inflammation and signs and symptoms of what is called ‘RA’, to which patients with a genetic predisposition are more susceptible. The 1987 classification criteria incorporated relatively late manifestations of the disease process such as damage and rheumatoid nodules; this means that there is a strong possibility that early RA is not classified as such. Not identifying and treating early RA could result in progression to severe destructive disease. The window-of-opportunity hypothesis suggests the presence of a period of...
time somewhere on this timeline in which a longstanding immunological benefit can be expected when the proper treatment is initiated.\textsuperscript{33} Withholding treatment until patients fulfil the 1987 criteria for RA, and keeping in mind the growing evidence for the benefit of early effective treatment, the window of opportunity might be (partly) missed. The BeSt study aimed at early treatment, including patients who had less than 2 years of arthritic symptoms, however, since patients were also required to fulfil the 1987 classification criteria, one may argue that many patients did not have ‘early RA’. Although in some patients remarkable results were observed, in many disease activity remained smouldering or flared and radiological damage progression continued to increase over time, possibly the result of a relatively late start of treatment. When exactly treatment has to start in patients with (undifferentiated) arthritis in order to achieve a long-lasting benefit and to prevent joint damage progression remains unclear. The PROMPT study shows that anti-CCP positive patients with inflammatory arthritis, not yet fulfilling the 1987 classification criteria, benefit from early treatment with methotrexate with suppression of disease activity and radiological damage progression.\textsuperscript{24} However, in most patients the symptoms progressed to ‘1987 classified RA’ after MTX was discontinued showing that early treatment with MTX was insufficient to change the disease course. The most effective early treatment has yet to be determined. To classify RA in an earlier phase of the disease, the 2010 classification criteria for RA were developed with the consequence of encouraging earlier initiation of treatment. Ideally, treatment should start immediately after the occurrence of the first immunological event that in time will lead to the progression of RA, or even better, treatment should prevent that event to happen. To do so, the challenge is to identify and understand pivotal events in the development of inflammatory arthritis. Once identified, the next step is to develop specific targeted treatment in order to prevent these master switches to occur.

Future challenges
To continue the followed road of improving treatment options and thereby improving the outlook and prognosis of recently diagnosed RA patients further unravelling of the pathophysiology, and as mentioned above, identification of the major pivotal events leading to RA is essential. Then we could enter a new era of targeted treatment leading towards cure and/or prevention of the disease. Until then, the available treatment options should be used in an optimal manner, which is challenging with the growing armamentarium of available therapies. Further implementation of early, aggressive targeted treatment aiming at remission is the first step towards optimising treatment. With the development of treatment recommendations an important start has been made, but still a large gain can be made here. Regular disease activity measurements should be the base of treatment decisions. The development of the 2010 ACR/EULAR criteria for RA made it possible to assess the efficacy of DMARDs and biologicals, alone or in combination, earlier in the disease course in a well-defined group, what will be translated to clinical practice the next decades. Future research will elucidate whether treatment initiation when these criteria are fulfilled is early enough or whether treatment should be initiated before this stage. Challenging is the development of effective therapeutic strategies in patients who cannot achieve or keep clinical remission with current therapies. The variety of clinical remission definitions all allow residual disease activity, potentially leading to joint damage progression, providing a rationale for aiming at radiological remission parallel to clinical remission in the future. However, first needs to be proven that radiological remission is treatable and that aiming at radiological remission has additional value in improving patients outcome above aiming at clinical remission.\textsuperscript{35} If that is the case, next challenges are the development of radiological remission criteria feasible for clinical practice, preferable combined with a clinical remission definition, to convince clinicians of the necessity of regular structured damage scoring and the implementation into clinical practice by arranging training in simple structured damage scoring systems like the simplified erosion and narrowing score world-wide. The clinician should continuously weigh the efficacy, side effects, risk for over- and undertreatment and costs of available treatment options in an evidence-based way, which is almost impossible with the massive and growing treatment possibilities. New trials with a dynamic design mimicking clinical practice like BeSt will add to the development of evidence-based strategies that can be incorporated in daily practice and can help the clinician in choosing optimal treatment. The exact role of the newer biologicals in treatment strategies is unclear. Of large value would be a clinical trial with a direct comparison of available biologicals, including TNF inhibitors, in early as well as in more established disease, preferable in a dynamic treatment design. The growing number of eligible drugs would make the inclusion of all candidates into a trial challenging. In the BeSt study treatment is individualised by making treatment decisions based on disease activity levels of the individual patient. Although partly tailored, all patients followed predefined treatment steps and the decision in all patients was based on the DAS with the cut-offs 2.4 and 1.6, ignoring the development of radiological joint damage progression. Tailor made treatment is necessary not only to prevent over- and undertreatment, but also for keeping health costs manageable. Further development of prediction models, probably by introducing genetic and biological risk factors instead of more clinical characteristics may contribute to more personalised treatment in the future. The difficulties lie in the identification of these important biological characteristics and feasibility for clinical practice.

Conclusion
This thesis describes several clinical aspects of modern RA treatment from the perspective of a randomised controlled trial comparing four different treatment strategies. Starting with combination therapy led to an earlier improvement of clinical characteristics with an advantage on joint damage progression until 5 years of follow-up compared to starting with monotherapy. With the availability of new treatment options, including biologicals, the early aggressive start of treatment and target-steered treat-
ment the outlook for recently diagnosed RA patients improved considerably the past few decades. Where treatment has changed from symptom control to more and more disease control over the past few decades, RA itself appears to have changed, leaving the traditional clinical picture of a chronically progressive, destructive disease. For a majority of patients, suppression of disease activity and radiological damage progression can effectively be achieved and clinical remission has become a realistic treatment goal. Clinical remission without DMARDs, which was found in up to 20% of patients, has become real now, coming close to cure. Further exploration of the biological and immunological background of RA and earlier start of more individualised aggressive treatment may change rheumatoid arthritis into a curable or even preventable disease in the future.

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**CHAPTER 14**

Nederlandse samenvatting
De BeSt studie

In de BeSt studie zijn 508 patiënten met recent gediagnosticeerde reumatoïde artritis (korter dan 2 jaar), welke voldeden aan de 1987 classificatie criteria van de American College of Rheumatology (ACR), gerandomiseerd in vier behandelstrategieën: 1. sequentiële monotherapie (n=126), 2. step-up combinatie therapie (n=121), beide startend met methotrexaat monotherapie, 3. initiële combinatietherapie met prednison en 4. initiële combinatietherapie met de tumor necrosis factor (TNF) alpha remmer infliximab (n=128). In alle behandelmengen werden patiënten behandeld volgens een stapsgewijze protocol strevend naar lage ziekteactiviteit. Elke 3 maanden werd de disease activity Score (DAS) bepaald. Bij een DAS van 2,4 of kleiner (lage ziekteactiviteit) werd de behandeling voortgezet en na 6 maanden afgebouwd tot een onderhoudsdosering. Bij een DAS groter dan 2,4 werd overgestapt op de volgende behandelmeng. Twintig ziekenhuizen in zuidwest Nederland namen deel aan de BeSt studie.

Primaire uitkomstmaten waren dagelijks functioneren, driemaandelijks gemeten met de health assessment questionnaire (HAQ), en progressie van gewrichtsschade, jaarlijks gemeten op röntgenfoto’s van handen, polsen en voeten met de Sharp-van der Heijde methode (SHS). Secundaire uitkomstmaten waren remissiepercentages en kwaliteit van leven. De resultaten van de eerste twee jaar lieten een snellere verbetering in ziekteactiviteit, dagelijks functioneren en kwaliteit van leven zien en minder progressie van gewrichtsschade in de initiële combinatietherapiegroepen (groep 3 en 4) ten opzichte van de initiële monotherapiegroepen (groep 1 en 2). Als gevolg van de continue metingen van ziekteactiviteit en 20 nodig aanpassing van de behandeling waren de klinische uitkomsten na een jaar vergelijkbaar in alle behandelgroepen en bleven stabiel gedurende 5 jaar. Na 5 jaar behandeling hadden de initiële combinatietherapiegroepen minder gewrichtsschade dan de initiële monotherapiegroepen. Een gedetailleerde analyse van de schadeprogressie per jaar liet zien dat het verschil in schadeprogressie van de initiële combinatietherapiegroepen t.o.v. de initiële monotherapiegroepen gebaseerd is op een verschil in schadeprogressie in het eerste jaar, waar de combinatietherapie groepen een snellere afname van ziekteactiviteit lieten zien. In de daaropvolgende jaren is de jaarlijkse radiologische progressiesnelheid gemeten met de SHS vergelijkbaar in alle groepen. Er waren geen duidelijke verschillen in toxiciteit gevonden tussen de behandelgroepen.

Het vaststellen van een behandeldoel en de associatie van ziekteactiviteit met klinische en radiologische uitkomsten

Veel wetenschappelijke studies hebben de associatie tussen ziekteactiviteit, functionele capaciteit en het optreden van gewrichtsschade aangetoond. Dit vormt de achtergrond van het vroeg inzetten van effectieve behandelstrategieën om ziekteactiviteit vroeg en adequaat te onderdrukken, zodat functionele beperkingen en gewrichtsschade zoveel mogelijk voorkomen kunnen worden. Vroeg in het ziekteloop worden functionele beperkingen vooral verklaard door actieve inflammatie (grotendeels reversibel), terwijl later in het ziekteloop gewrichtsschade meer gaat bijdragen aan beperkingen in functioneren (grotendeels irreversibel).

Strategie studies

De effectiviteit van behandelingen wordt vaak onderzocht in gerandomiseerde, dubbelblind placebo-gecontroleerde trials (RCTs). Deze studies hebben veelal een statisch design waarin een directe vergelijking van verschillende (combinaties) van geneesmiddelen met de individuele combinaties dat specifiek gericht zijn op het immuunsysteem (biologicals) en strikte en regelmatige meting van ziekteactiviteit met aanpassing van medische toezicht tot het behandeldoel behaalde (‘tight control’ en ‘treat to target’) hebben bijgedragen aan deze verbetering in prognose en hebben geleid tot een verschuiving in behandelparadigma’s. In hoofdstuk 1 wordt een algemene inleiding op het proefschrift gegeven. Hoofdstuk 2 geeft een overzicht van klinische presentatie, diagnose en behandelmogelijkheden voor RA patiënten waarin het belang van vroege verwijzing naar een reumatooloog benadrukt wordt om het vroeg starten van effectieve behandeling mogelijk te maken.

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Het vaststellen van een behandeldoel en de associatie van ziekteactiviteit met klinische en radiologische uitkomsten

Veel wetenschappelijke studies hebben de associatie tussen ziekteactiviteit, functionele capaciteit en het optreden van gewrichtsschade aangetoond. Dit vormt de achtergrond van het vroeg inzetten van effectieve behandelstrategieën om ziekteactiviteit vroeg en adequaat te onderdrukken, zodat functionele beperkingen en gewrichtsschade zoveel mogelijk voorkomen kunnen worden. Vroeg in het ziekteloop worden functionele beperkingen vooral verklaard door actieve inflammatie (grotendeels reversibel), terwijl later in het ziekteloop gewrichtsschade meer gaat bijdragen aan beperkingen in functioneren (grotendeels irreversibel).

Hoofdstuk 2

Wordt een algemene inleiding gegeven. Hoofdstuk 3 worden de belangrijkste resultaten van recente studies in de behandeling van RA samengevat. De BeSt studie (acroniem voor Behandel Strategieën) waarop dit proefschrift is gebaseerd is een voorbeeld van een strategie studie.
In de BeSt studie werd gestreefd naar lage ziekteactiviteit (DAS ≤2,4). Dit heeft geleid tot een gemiddelde HAQ score van 0,58 na 5 jaar behandeling. Om de associatie tussen ziekteactiviteit en functioneren in meer detail te bestuderen, is in hoofdstuk 6 een longitudinale analyse van ziekteactiviteit en functioneren verricht. Met interactietermen is gekeken of de associatie tussen een verandering in DAS en een verandering in HAQ afhankelijk is van de follow-up duur en het absolute DAS niveau. We toonden aan dat een grotere afname in DAS geassocieerd is met een grotere afname in HAQ. Deze associatie is afhankelijk van het absolute DAS niveau, maar niet van de follow-up duur. Volgens het model is een afname in DAS van 2,5 naar 1,5 geassocieerd met een grotere toename in HAQ score van 0,58 na 5 jaar behandeling. Dit heeft geleid tot een gemiddelde HAQ score van 0,59 na 8 jaar behandeling. Het is veelbelovend dat na 8 jaar follow-up in de BeSt studie de HAQ stabiel blijft met een gemiddelde (SD) van 0,59 (0,59). Hiermee zou op een directe wijze aangetoond kunnen worden wat de winst van streven naar remissie zou zijn. Eerdere studies hebben laten zien dat er, na een vroege afname van HAQ door het starten van behandeling, gemiddeld na 3-6 jaar een toename in HAQ optreedt. Waarschijnlijk wordt dit verklaard door irreversibele toename van fungeerende beperkingen. Door aanhoudende targeted treatment en het beperken van gewrichtsschade kan irreversibele toename van functionele beperkingen uitgesteld worden en in een subgroep van patiënten misschien zelfs voorkomen worden. Het is veelbelovend dat na 8 jaar fol-

Remissie

In hoofdstuk 7 zijn 13 remissiedefinities met elkaar vergeleken, waaronder vier varianten van de 2011 ACR/EULAR remissie criteria: de criteria voor de klinische praktijk en klinische trials, zowel met 28/28 als met 68/66 gewrichtsscores. De ACR/EULAR klinische trial definitie met 68/66 gewrichtsscores bleek de meest strikte van alle definities. Deze definitie was geassocieerd met een grotere toename van functionele beperkingen, maar het was onbekend hoe de vergelijkbaarheid was. Alhoewel in individuele patiënten de VAS scores variëren, waren de verschillen als onderdeel van een ziekteactiviteitsscore klein, voor lage ziekteactiviteit schadeprogessie
Hoofdstuk 8 en 9

Het stoppen van medicatie

Behandeling volgens het ‘treat to target’ principe, met een vast behandeldoel en aanpassing van de behandeling tot dat het doel bereikt is, wordt geadviseerd in RA patiënten. Er bestaan echter geen richtlijnen over wat te doen als het behandeldoel bereikt is. Moet medicatie voortgezet worden of kan medicatie afgebouwd worden of zelfs helemaal worden gestopt? Stoppen heeft als voordelen dat er geen bijwerkingen meer kunnen optreden, patiënten geen medicatie hoeven in te nemen en de kosten beperkt blijven. Aan de andere kant kan het stoppen van medicatie bijdragen aan een versterking van de ziekteactiviteit en het staken van alle medicatie bij patiënten in langdurige klinische remissie. Het stoppen van infliximab bij patiënten met langdurig lage ziekteactiviteit

Een TNF remmer gecombineerd met methotrexaat kan ziekteactiviteit snel en effectief onderdrukken en gewrichtsschade voorkomen, maar het doel is om de behandeling zo snel mogelijk te stoppen. Daarom zou het stoppen van een TNF remmer voordelig kunnen zijn. In de BeSt studie werd infliximab gestopt als patiënten gedurende 6 maanden lage ziekteactiviteit hadden. In hoofdstuk 8 is het staken van infliximab nader geanalyseerd, zowel in patiënten die direct bij aanvang van de studie met infliximab zijn gestart (groep 4) als in patiënten die medici het staken van medicatie voortgezet wellicht aanmoedigen. Daarom zou het stoppen van anti-TNF remmers voordelig kunnen zijn voor de behandeling van RA. In de BeSt studie zijn de remissiepercentages vanaf het begin van de studie hoger dan op voorhand verwacht in deze populatie van patiënten met recent gediagnosticeerde actieve RA. Na 5 jaar was in alle behandelgroepen 48% van de patiënten in klinische remissie, gedefinieerd als DAS ≤2,4. Na het 3e jaar werd het mogelijk het snel stoppen van medicatie te staken bij patiënten die langdurig in remissie waren (⋯ maanden). De laatste effectieve DMARD werd direct herstart als remissie verloren ging. Na 5 jaar was 10-19% in medicatievrije remissie (completers analyse) met een mediane duur van 23 maanden (hoofdstuk 4). In hoofdstuk 8 zijn de patiënten met medicatievrije remissie in detail bestudeerd. Na het herstarten van de laatste DMARD hadden geen voorspellende waarde. Na het herstarten van de behandeling in verband met een flare bereikten de deelnames binnen 3-6 maanden weer remissie. De herstarters hadden iets meer progressie van gewrichtsschade dan de patiënten die niet in remissie behielden na het staken van de medicatie. Naast de tijdelijke toe-
aan bijgedragen. Een gecontroleerde stop studie zou nodig zijn om te onderzoeken of de
flares en de kleine hoeveelheid gewrichtsschade ook waren opgetreden als de medicatie
voorgezet zou zijn. Een dergelijke gerandomiseerde studie loopt momenteel in Neder-
land, op initiatief van de NVR (POEET-studie), waarbij anti-TNF gecontroleerd gestaakt
wordt in patiënten in langdurige klinische remissie. De conventionele DMARDs worden in
 deze studie gecontinueerd. Destijds, toen biologicals nog niet beschikbaar waren, hebben
Ten Wolde, et al. (Lancet, 1996) een dergelijke placebo-gecontroleerde stop-studie verricht
waarbij alle medicatie in klinische remissie met een lange ziek-
teduur, waarin stoppen met medicatie geassocieerd was met meer flares. Alhoewel de BeSt
populatie duidelijk verschilt van deze populatie, suggereren de resultaten van Ten Wolde,
et al. dat door het stoppen van de medicatie de hoeveelheid flares waarschijnlijk is toe-
genomen in de BeSt studie. Aan de andere kant laat deze studie zien dat een groot deel
van de opvallingen ook zou zijn opgetreden als de medicatie gecontinueerd zou zijn.
Met deze overwegingen in het achterhoofd kan het stoppen van medicatie in patiënten
in langdurige remissie overwogen worden. Dit moet wel gebeuren onder strikte controle
van ziekteactiviteit en als een gezamenlijke beslissing van reumatoloog en patiënt; na een
zorgvuldige afweging van voor- en nadelen.

Klinische synovitis versus progressie van gewrichtsschade

De relatie tussen ziekteactiviteit, dagelijks functioneren en progressie van gewrichtsschade
is uitgebreid onderzocht en vormt de basis van huidige behandelstrategieën. Alhoewel het
een algemeen aanvaard concept is, hebben slechts weinig studies de associatie tussen
klinische symptomen van synovitis (pijn, zwelling) en progressie van gewrichtsschade op
individueel gewrichtsniveau met een goede methodologie onderzocht. In hoofdstuk 10 zijn
bevindingen van lichamelijk onderzoek van zwelling en pijn uit het eerste jaar gere-
lateerd aan progressie scores van erosies en gewrichtspleeptvernarvingen binnen het
zelfde gewricht, vastgesteld op röntgenfoto’s van baseline en na 1 jaar follow-up. Zwelling
en pijn waren beiden onafhankelijk geassocieerd met progressie van gewrichtsschade op
gewrichtsniveau met vergelijkbare odds ratios. De associaties waren ongeveer even sterk
voor erosies, gewrichtspleeptvernarving en totale SHS progressie per gewricht. Ondanks
dat een pijnlijk gewricht soms wordt beschouwd als een minder specifieke marker voor
synovitis dan een gezwollen gewricht, laat hoofdstuk 10 zien dat het vaststellen van pijn
toegevoegde waarde heeft naast het vaststellen van zwelling alleen. Hoe langer zwelling
en pijn aanwezig is, hoe groter de kans op progressie. Deze dosis-response relatie werd
vastgesteld in het eerste jaar, wat het belang van vroege effectieve doelgerichte behande-
ing onderstrept. De associatie is sterker in de handen dan in de voeten, waarschijnlijk
doordat het onderzoeken van gewrichten in de voeten moeilijker is.

Alhoewel er een duidelijke relatie tussen klinische symptomen van synovitis en schade-
progressie bestaat, verklart dit slechts een deel van de totale variabiliteit in gewrichts-
schade. Vele bekende en onbekende factoren bepalen het risico op het optreden van
gewrichtsschade: patiëntkenmerken, lokale factoren in het gewricht en behandeling. In
hoofdstuk 10 werd gezien dat bekende voorspellers voor gewrichtsschade, zoals anti-
stoffen (anti-CCP en reumafactor), acute fase eiwitten, leeftijd, de totale hoeveelheid
gewrichtsschade en de SHS score per gewricht bij aanvang van de studie, naast zwelling
en pijn ook gerelateerd zijn aan progressie van erosies en gewrichtspleeptvernarving op
individueel gewrichtsniveau. Naast deze factoren vergroot de aanwezigheid van zwel-
ling en pijn het absolute risico op progressie met de bijbehorende odds ratios. In hoofdstuk 10 laten we tevens zien dat behandeling de associatie tussen klinische
symptomen van synovitis en de progressie van gewrichtsschade beïnvloedt, zowel bij
zwelling als bij pijn. In patiënten die initieel behandeld werden met de combinatie
metho-
trexaat en infliximab (groep 4) werd geen significante associatie tussen synovitis
symptomen en schadeprogressie gevonden, in tegenstelling tot de andere 3 behandel-
groepen. Deze resultaten bevestigen de dissociatie tussen klinische symptomen van
inflammatie en progressie van gewrichtsschade op gewrichtsniveau, welke op patiënt-
niveau reeds beschreven was en onderstrepen het belang van het pro-inflammatoire
cytokine TNF αfa in de pathofysiologie van gewrichtsschade.

Het vaststellen van progressie van gewrichtsschade in de klinische praktijk

Het regelmatig bepalen van gewrichtsschadeprogressie zou een standaard onderdeel
moeten zijn bij het evalueren van een behandeling in de klinische praktijk. Een toe-
name in gewrichtsschade gemeten op röntgentofo’s kan, onafhankelijk van de klinische
response, een verandering van medicatie rechtvaardigen, aangezien dit op termijn kan
leiden tot functionele beperkingen. Toename van gewrichtsschade zonder objecti-
veerbare klinische symptomen zou de enige hint kunnen zijn voor de aanwezigheid
van subklinische inflammatie bij onvoldoende effectieve behandeling. Idealiter wordt
progressie van gewrichtsschade vastgesteld met een gestructureerde scoringsmethode.
Veel gebruikte methodes, zoals de Sharp-van der Heijde methode en de Larssen score,
uitgebreid, kosten relatief veel tijd en vereisen training, wat het gebruik in de klini-
sche praktijk belemmert. In hoofdstuk 11 wordt een vergelijking gemaakt tussen de uit-
gebreide, goed gevalideerde Sharp-van der Heijde score (SHS) en de ‘simplified erosion
and narrowing score’ (SENS). SENS laat de gradering per gewricht achterwege, is onge-
veer 3 keer sneller dan de SHS en is makkelijker te leren. De resultaten laten zien dat SENS
een waardevolle gestructureerde methode is om gewrichtsschade vast te stellen in de
klinische praktijk doordat de methode sneller is. Voor het gebruik in onderzoek is SENS
minder geschikt omdat de methode minder sensitief is en het onderscheidend vermoo-
gen kleiner zal zijn door het weglaten van de gradering per gewricht.

Cardiovaseculaire ziekte

Er wordt gedacht dat het (patho)fysiologische fenomeen inflammatie een rol speelt in
diverse ziekten, waaronder atherosclerose. RA is geassocieerd met een verhoogd risico
op cardiovasculaire ziekten, vergelijkbaar met patiënten met diabetes mellitus. Naast
een hogere prevalentie van traditionele cardiovasculaire risicofactoren, dragen overlapp-
ende inflammatoire pathways waarschijnlijk mee aan het verhoogde risico op cardio-
vasculaire aandoeningen in RA. Door dit verhoogde risico is het belangrijk extra aan-
dacht te besteden aan traditionele risicofactoren, waaronder veranderingen in lifestyle en de optimale behandeling van hypertense, hypercholesterolemie en diabetes mellitus. Bovendien is het belangrijk om de rol van RA behandeling in relatie tot cardiovasculaire risicofactoren en –ziekten in ogenschouw te nemen. Hoofdstuk 12 laat een associatie tussen ziekteactiviteit en bloeddruk zien. Aanhoewel het effect weliswaar klein is, werd de associatie gevonden voor zowel systolische als diastolische bloeddruk, suggereerend dat een lager niveau van inflammatie samengaat met een gunstiger cardiovasculair risicoprofiel. Er werd tevens een afname in systolische en diastolische bloeddruk gevonden in patiënten die behandeld zijn met de initiële combinatie methotrexaat en de TNF remmer infliximab. In de andere behandelgroepen werd geen bloeddrukdaling gezien. Deze resultaten moeten voorzichtig geïnterpreteerd worden omdat de BeSt studie niet opgezet is om bloeddrukverschillen te meten en de observaties zijn gebaseerd op enkelvoudige bloeddrukmetingen zonder meetprotocol. Desondanks kan dit, ‘dankzij’ het hoge risico op cardiovasculaire ziekten in RA, een klinisch relevante observatie zijn.

Vroeg starten?
De BeSt studie illustreert dat met effectieve behandeling vroeg in het ziektebeloop een significante verbetering in klinische parameters en het beperken van progressie van gewrichtsschade haalbaar is in een groep patiënten met actieve RA. Bij aanvang van de studie voldeden alle patiënten aan de 1987 classificatie criteria voor RA. De ontwikkeling van RA kan geïnterpreteerd worden op een tijdslijn, beginnend met een onbekend pathofysiologisch event, via de vorming van auto-antistoffen, via subklinische inflammation tot een combinatie van symptomen en eigenschappen dat ‘RA’ wordt genoemd, waarbij deze ontwikkeling vaker voorkomt bij dijgenen met een genetische predispositie voor RA. Onderdeel van de 1987 classificatie criteria zijn relatief late manifestaties van de ziekte, zoals gewrichtsschade en reumanoduli, waarvoor de diagnose in een vroeg stadium gemist kan worden. Het niet identificeren en daardoor niet behandelen van vroege RA kan leiden tot progressie naar een ernstige destructieve ziekte. De window-of-opportunity hypothese suggeereert het bestaan van een periode ergens op deze tijdslijn waarbij met de juiste behandeling een blijvend immunologisch voordeel bewerkstellig kan worden. Met het wachten met behandelen tot patiënten aan de 1987 classificatie criteria voldoen wordt de window-of-opportunity mogelijk (deels) gemist. In de BeSt studie werd gestreefd naar vroege behandeling in patiënten die minder dan 2 jaar klachten van artritis hebben, maar doordat ze aan de 1987 classificatie criteria moesten voldoen was een deel van de patiënten het stadium van vroege RA al gepasseerd. Ondanks dat er bij een aantal patiënten opvallende behandelterug(valen) werd gezien, bleef bij veel patiënten de ziekte sluimeren en bleef radiologische schade ontstaan. Wanneer behandeling gestart moet worden in patiënten met ongedifferentieerde artritis om een langdurig voordeel te bewerkstelligen en gewrichtsschade te voorkomen blijft onduidelijk. De PROMPT studie heeft laten zien dat in anti-CCP positieve patiënten met artritis die nog niet aan de 1987 criteria voldeden baat hebben bij vroege behandeling met methotrexaat waarmee ziekteactiviteit en radiologische progressie onderdrukt kunnen worden. De meeste patiënten ontwikkelden echter alsnog RA volgens de 1987 criteria na het staken van methotrexaat, wat laat zien dat methotrexaat onvoldoende in staat is het ziektebeloop te beïnvloeden. De meest effectieve therapie in dit ziektebeloop moet nog worden vastgesteld. Om RA eerder te kunnen classificeren zijn de 2010 classificatie criteria ontwikkeld, mede om vroegere behandeling te stimuleren. Idealerl zou behandeling gestart moeten worden direct na het optreden van de eerste immuno- logische verandering welke op den duur leidt tot de progressie naar RA, of nog beter, behandeling zou deze verandering moeten voorkomen. Voordat dit bereikt is, ligt de uitdaging in het identificeren en begrijpen van de essentiële stappen in de pathofysiologie van RA. De volgende stap is dan de ontwikkeling van gerichte therapie die het opzien van deze masterswitches kan voorkomen.

Toekomstperspectieven
Om de ingezette weg van het verbeteren van behandelmogelijkheden en daarmee de prognose van recent gediagnosticeerde RA te verbeteren voort te zetten is het essenti-eel meer inzichten in de pathofysiologie te krijgen, en zoals reeds genoemd, de noodzakelijke stappen die tot RA leiden te identificeren. Dan kan een fase betreden worden waarbij gerichte therapie kan leiden tot de genezing en/of preventie van de ziekte. Tot dan moeten de bestaande therapieën zo efficiënt mogelijk toegesneden worden, wat niet makkelijk is met het steeds groter aantal therapieën in het arsenaal van de reumatoloog. Verdere implementatie van vroege doelgerichte therapie streven naar klinische remissie is de eerste stap in de optimalisatie van behandeling. Met de ontwikkeling van behandeldrichtlijnen is een goede stap voorwaarts gezien, maar er is op dit terrein nog veel winst te behalen. Het frequent meten van ziekteactiviteit zou de basis van behandelbe- slissingen moeten vormen. De 2010 ACR/EULAR classificatie criteria voor RA hebben de weg vrijgemaakt voor studies naar het vroeger inzetten van DMARDS en biologicals, alleen of in combinatie, in een duidelijk gedefinieerde groep, waardoor het van toepassing kan worden naar de klinische praktijk in de komende decennia. Toekomstig onderzoek zal moeten uitwijken of het starten van de behandeling als aan deze criteria voldaan wordt vroeg genoeg of dat behandeling nog eerder gestart zou moeten worden. Een andere uitda- ging is om effectieve strategieën te ontwikkelen in de patiënten bij wie het nog niet lukt klinische remissie te behalen of behouden. Alle bestaande klinische remissiedefinities laten residuele ziekteactiviteit toe, potentieel leidend tot gewrichtsschade, een argument om in de toekomst naar klinische remissie te streven parallel aan klinische remissie. Eerst moet worden vastgesteld dat radiologische remissie te realiseren is met behandeling en dat het streven naar radiologische remissie leidt tot betere uitkomsten voor patiënten dan het streven naar klinische remissie alleen. Als dat zo blijkt te zijn, zijn de volgende uitdagingen het opstellen van een radiologische remissie definitie, bij voorkeur gecombineerd met een klinische definitie, het overtuigen van cliënten te zijnde nut van regelmatig en gestructureerd meten van gewrichtsschade en het implementeren in de klinische praktijk door wereldwijde training in relatief eenvoudige gestructureerde meetmethoden zoals de SENS.
De reumatoloog heeft de taak een continue afweging te maken tussen effectiviteit, bijwerkingen, risico op over- en onderbehandeling en kosten - een bijna onmogelijke opgave met de steeds verder toenemende behandelopties. Nieuwe strategie studies met een dynamische opzet die de klinische praktijk zoveel mogelijk benaderen zoals de BeSt studie, zullen leiden tot nieuwe evidence-based strategieën voor de klinische praktijk die de reumatoloog kan ondersteunen in het kiezen van de optimale behandeling. Het is onduidelijk wat de precieze rol van de nieuwere biologicals in behandelstrategieën zou moeten zijn. Een klinische studie waarin een directe vergelijking wordt gemaakt tussen de beschikbare biologicals, inclusief anti-TNF, bij voorkeur in een dynamisch design zou van grote waarde zijn, zowel in vroege als in meer gevorderde ziekte. Het groeiende aantal beschikbare middelen maakt de inclusie van alle potentiele kandidaten in één studie moeilijk.

In de BeSt studie is er deels sprake van behandeling toegespitst op de individuele patiënt, omdat behandelbeslissingen genomen werden op basis van individuele metingen van ziekteactiviteit. Ondanks dat de behandeling deels aangepast werd op het individu, volgden alle patiënten een protocol met vooraf vastgestelde behandelstappen en de veranderingen in medicatie werden in alle patiënten gebaseerd op DAS cut-offs van 2,4 en 1,6, waarbij het optreden van radiologische schade buiten beschouwing werd gelaten. Gepersonaliseerde behandeling is nodig om onder- en overbehandeling te voorkomen en om de kosten van de gezondheidszorg beheersbaar te houden. Verdere ontwikkeling van voorspelmodellen, mogelijk met name door het introduceren van genetische en biologische risicofactoren in plaats van het uitbreiden van predictiemodellen met klinische parameters, kan bijdragen aan behandeling die meer gericht is op het individu in de toekomst. De moeilijkheid ligt in de identificatie van deze belangrijke biologische kenmerken en de toepasbaarheid hiervan in de klinische praktijk.

Conclusie

Dit proefschrift beschrijft diverse aspecten van de moderne behandeling van RA vanuit het perspectief van een gerandomiseerde gecontroleerde studie waarin vier verschillende behandelsstrategieën worden vergeleken. Starten met combinatietherapie leidt tot een vroegere verbetering van klinische uitkomsten met een gunstig effect op de progressie van gewrichtsschade na 5 jaar follow-up ten opzichte van starten met monotherapie. Met de beschikbaarheid van nieuwe behandelmogelijkheden, waaronder biologicals, de vroege agressieve start van behandeling en doelgerichte behandeling zijn de vooruitzichten voor patiënten met recent gediagnosticeerde RA aanzienlijk verbeterd de laatste decennia. Het doel van behandeling is veranderd van symptoombestrijding naar het steeds beter controleren van de ziekte; RA zelf lijkt hierdoor veranderd en neemt steeds meer afstand van het traditionele klinische beeld van een chronisch progressieve, destructieve ziekte. Onderdrukking van ziekteactiviteit en schadeprogressie kan in de meerderheid van de patiënten worden bereikt en klinische remissie is een realistisch behandeldoel geworden. Medicatievrije remissie, wat werd gezien in bijna 20% van de patiënten, is realiteit geworden, waardoor genezing benaderd wordt. Verdere exploratie van de biologische en immunologische achtergrond van RA en het vroeger inzetten van agressieve therapie meer gericht op het individu kan RA veranderen in een te genezen of zelfs te voorkomen ziekte in de toekomst.
Appendix
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