Targeted treatment in early rheumatoid arthritis

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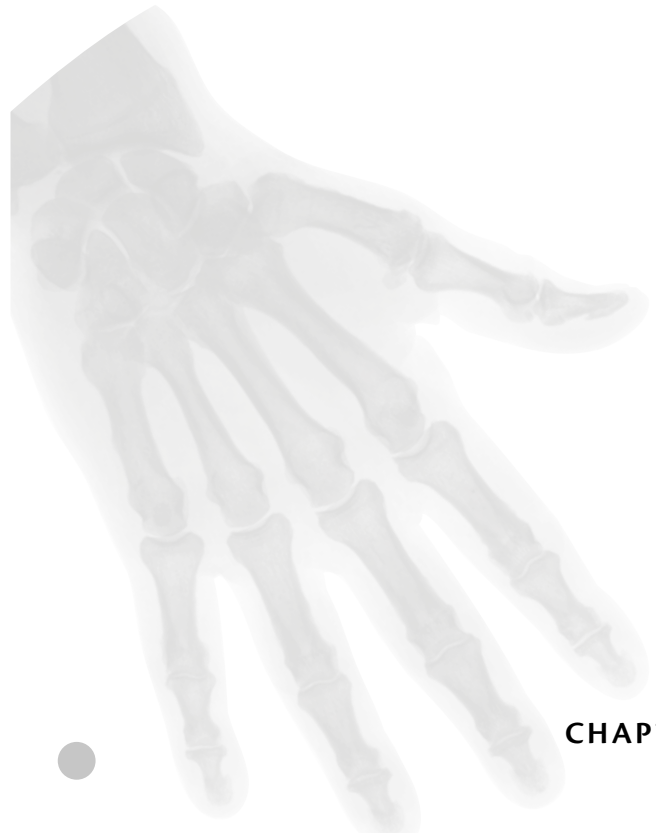

CHAPTER 1

General Introduction

GENERAL INTRODUCTION

This thesis is based on data of the BeSt study (Dutch acronym for Behandel Strategieën; treatment strategies), a large randomised controlled trial comparing four different treatment strategies in patients with recent-onset rheumatoid arthritis.[1-3] 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 di-arthrodial 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[4] 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.[5]

Joint damage

Radiological damage progression assessed on plain x-rays is one of the main outcomes in rheumatoid arthritis (RA) treatment.[6] 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[5,7,8] 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[9] and Larsen[10] and its modifications are most often used. The Sharp-method, modified by Van der Heijde[11] is well-validated and commonly used in clinical trials. In total, 32 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.[12] 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.[13,14] Joint damage progression has a skewed distribution: a minority of patients shows marked progression, whereas the majority shows little or no progression. Therefore by 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.[14] The Smallest Detectable Change can be used as a cut-off for distinguishing measurement error form 'real' progression.[15]

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.[16] 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.[17] Later, Siegert, et al validated the Dutch version of the HAQ.[18] With the HAQ patients are asked whether they are able to perform different daily activities on 8 domains: dressing and grooming, arising, eating, walking, hygiene, reach, grip and 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).[19] 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, pericarditis, lymphadenopathy, amyloidosis, peripheral neuropathy, vasculitis and splenomegaly.[20] Furthermore, rheumatoid arthritis is associated

with a higher prevalence of cardiovascular morbidity and mortality than in the general population.[21-25] 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.[26]

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%).[27] 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.[28]

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.[29] 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.[30] 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.[31]

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.[32] 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,[33] and is predictive for a more severe disease course.[34] 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.[35] There is increasing evidence that ACPA play a pathogenic role in rheumatoid arthritis,[36,37] although the exact mechanism is unknown. Both anti-CCP and rheumatoid factor can be present years before onset of the disease.[38]

Classification and diagnosis

The term 'Rheumatoid Arthritis' was first used in 1859, by the British Rheumatologist Alfred Baring Garrod.[39] 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'.[40] Until May 2010, the classification criteria formulated by the American College of Rheumatology (ACR) in 1987 for rheumatoid arthritis[41] 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 (MCP, PIP) or wrists, 4. symmetrical 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.[42] 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.[43] 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.[44]

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.[45,46] 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[47] due to its clinical and radiological efficacy,[48-52] acceptable long-term toxicity profile[53], high retention rates[54] 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.[55-57] The most common side effects are reversible liver toxicity and gastro-intestinal complaints, which can be reduced by dose reduction and/or subcutaneous use, and by concomitant use of folic acid, recommended in a dose of at least 5 mg per week.[58] 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,[59] or in combination with other DMARDs,[60-63] although the additional value remains controversial.[63-65] 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.[52,66,67] 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, asymptomatic transaminase elevations, skin rash and myelotoxicity.[52]

Other, less commonly used DMARDs are the antimalarials hydroxychloroquine and chloroquine (favourable safety profile, but limited efficacy as monotherapy),[68-70] ciclosporin A (positive effect on clinical and radiological outcomes, unfavourable toxicity profile with renal toxicity and hypertension),[71-75] intramuscular gold (good efficacy, slow mode of action, probably more toxicity)[76,77] and azathioprine (moderate clinical efficacy, radiological efficacy inconclusive, unfavourable toxicity profile).[78-80]

Corticosteroids

In 1949, Hench, et al. described the beneficial effect of glucocorticoids on the symptoms of RA.[81] Since then, several randomised trials showed the efficacy of low-dose glucocorticoids (<10 mg) on clinical outcomes and on inhibiting joint destruction, alone,[82] and in addition to DMARD therapy.[83-85] 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,[86] 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.[87] 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.[88]

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-a.) 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-a. type II receptor/IgG1 fusion protein), adalimumab (humanized monoclonal antibody against TNF-a.), 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[57,89-93] and in early RA.[55,94-96] 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.[97,98] Due to high costs of anti-TNF therapy[99] 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.[100] 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.[101]

Controversies exist on whether anti-TNF increase the risk for serious infections.[102-105] 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.[102,105,106]
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.[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),[108] rituximab (B-cell depleter, anti-CD20),[109,110] abatacept (blocks CD80/CD86:CD28 costimulatory signal required for full T-cell activation),[111,112] and tociluzimab (anti-IL6).[113-116] A variety of other targets are currently under investigation: e.g. the inhibition of various kinases.[117] Anti-TNF is currently the first-choice biological for RA, due to its efficacy and longer experience.[118] Despite the remarkable response on anti-TNF treatment, approximately 1/3 of patients fail to respond on anti-TNF.[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[57,63,89-93] 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[120,121] and prevent joint damage progression.[43,122] 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.[43] These findings support the intriguing window-of opportunity hypothesis, which was first formulated during the 1990s.[123,124] 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 background 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.[125] 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.[126]
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.[127] 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.[128-135]
The BeSt 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.[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.[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)[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: $0.5398\sqrt{(RAI)} + 0.06465(SJC44) + 0.330\ln(ESR) + 0.00722(VAS)$.
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.[140,141] 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),[142] the clinical disease activity index (CDAI)[143] and the simplified disease activity index (SDAI).[144] 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.[143-146] 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,[147] 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.[148]

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.[1] 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.[2] 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.[3]

The prolongation of three-monthly follow-up visits until 5 and eventually until 10 years of follow-up in the BeSt study provides 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 and 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.

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