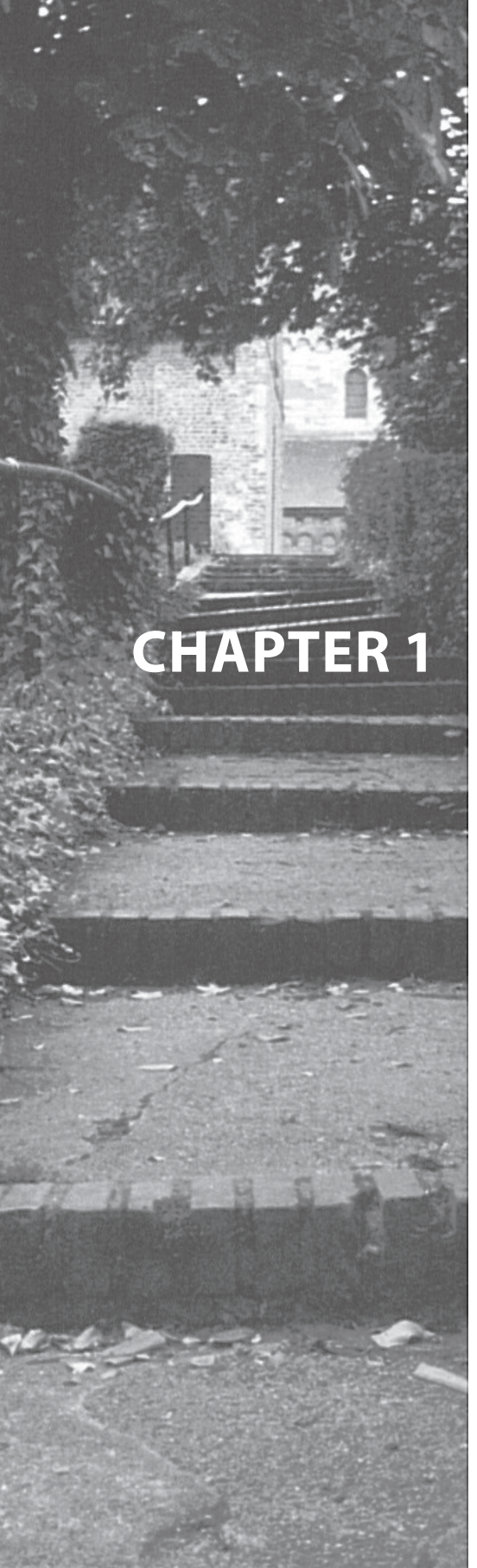

CHAPTER 1 General introduction

RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a systemic inflammatory disease with a potentially chronic and disabling disease course. It is characterised by a symmetric poly-arthritis most commonly affecting small joints in hands and feet.[1] Chronic inflammation causes damage of bone and joint tissues, potentially resulting in functional disability, work disability and social and mental problems.[2-5] Extra-articular manifestations such as cardiovascular disease, interstitial lung disease and rheumatoid vasculitis may shorten life expectancy, although with current treatment strategies their occurrence is declining.[1]

RA affects approximately 0.5-1% of the population of industrialized countries and most often women. The onset of symptoms often lies between 40 and 60 years.[6] It is an auto-immune disease, partly caused by genetic factors and partly by environmental factors, such as smoking.[1]

The classic auto-antibody in RA is rheumatoid factor (RF), consisting of immunoglobulins of all isotypes directed against the Fc fragment of IgG.[7] The most important auto-antibodies for clinical practice nowadays are those directed against anti-citrullinated proteins (ACPA). With a specificity of about 90-97%, ACPA have a higher specificity than RF. Their presence has been shown years before symptoms of arthritis develop.[8] In patients with undifferentiated arthritis (UA), presence of ACPA has shown to be predictive for the development of RA,[9,10] and in UA as well as established RA, presence of ACPA is associated with worse disease outcomes such as functional disability and joint damage progression.[11]

CLASSIFICATION OF RA

In 2010 new American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA are proposed to substitute the 1987 ACR classification criteria.[12,13](table 1) As many studies have shown that RA patients benefit from early introduction of disease modifying anti-rheumatic drugs (DMARDs)[14-17], these new criteria were designed with the aim to identify and consequently treat RA patients earlier in the disease course. Recent data have shown that the 2010 criteria indeed classify more patients as RA in an earlier phase of the disease than the 1987 criteria, and their sensitivity seems to be higher. The potential downside is that their specificity is lower, meaning that more patients are wrongly classified and treated as RA, while actually having another disease.[18,19]

Table 1: The 2010 ACR/EULAR classification criteria for rheumatoid arthritis.[13]

Target population: patients who 1) have at least 1 joint with definitive clinical synovitis 2) with the synovitis not better explained by another disease A score ≥ 6/10 is needed for classification as RA	
	Score
Joint involvement	
1 large joint	0
2-10 large joints	1
1-3 small joints	2
4-10 small joints	3
> 10 joints (at least 1 small joint)	5
Serology	
Negative RF *and* negative ACPA	0
Low-positive RF *or* low-positive ACPA	2
High-positive RF *or* high-positive ACPA	3
Acute phase reactants	
Normal CRP *and* normal ESR	0
Increased CRP *or* increased ESR	1
Symptom duration	
< 6 weeks	0
≥ 6 weeks	1

ACPA, anti-citrullinated protein antibodies; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor.

TREATMENT OF RA

During the last decades, dramatic changes have taken place in the treatment of RA. Treating patients earlier in disease course, using combination treatment, using tight control treatment strategies and the introduction of biological agents have resulted in spectacular improvements in disease outcomes.

Many trials in patients with recent-onset RA, often defined as a symptom duration of less than two years, have shown that early introduction of DMARDs more effectively suppresses disease activity, preserves functional ability and slows down radiological damage progression than delayed start of treatment.[14,17] Even more studies suggest the benefit of starting DMARD combination therapy, in particular together with glucocorticosteroids, instead of monotherapy on similar disease outcomes.[20-22] The concept of tight control treatment, targeted at a predefined treatment goal such as a low disease activity, has also been shown to be superior to conventional non-targeted ways of treating patients.[23] Finally, the introduction of biological agents in the 1990s has improved disease outcomes. Combining a DMARD with a biological agent has been shown to be more effective than DMARD-monotherapy [13,16,24,25]

or multiple DMARDs.[26] The EULAR recommendations for the management of RA recommend to start DMARD-monotherapy as soon as RA is diagnosed, to steer treatment at low disease activity or even remission, to expand to combination therapy as soon as monotherapy seems to fail and to switch to combination therapy with a biological agent, anti-TNF alpha being first choice, as soon as the treatment target is not reached with multiple DMARDs.[27] Although biological agents are very effective, they are also expensive and may have (infectious) side effects [28], making the need to search for less expensive alternatives ongoing. Treatment combinations including glucocorticosteroids may be one of those alternatives. Low dose glucocorticosteroids have previously been shown to suppress radiological joint damage progression when used as monotherapy and in combination with a DMARD.[29-31] Adding a tapered high dose of prednisone to multiple DMARDs has even been shown to be equally effective as methotrexate (MTX) in combination with infliximab in terms of controlling disease activity and suppressing radiological progression.[16]

Although both doctors and patients have concerns about the side effects of glucocorticosteroids, such as the enlarged risk of cardiovascular disease, diabetes and osteoporosis,[32] there is, at least on short term, no clear evidence that low doses of glucocorticosteroids cause more side effect than placebo treatment. There has even been a suggestion that low dose glucocorticosteroids result in fewer side effects when given as part of combination therapy.[33,34] In the EULAR recommendations for the management of RA (2010) it is recommended to add low to moderate high doses of glucocorticosteroids to initial DMARD mono- or combination therapy, but it should be tapered as rapidly as clinically feasible.[27]

DISEASE OUTCOMES

Due to improving treatment strategies, treatment goals have changed over time and the bar has been set higher and higher. Nowadays we are not satisfied until total disease control has been achieved, by trying to rapidly lower disease activity aiming for remission and even drug free remission, trying to prevent radiological damage progression, to preserve functional and working ability and to normalize quality of life.

In clinical trials, remission and drug free remission have become attainable treatment goals, although not for all patients.[35-37] Several definitions for remission have been used. The Disease Activity Score (DAS), a composite score including a swollen joint count, a tender joint count (using the Ritchie Articular Index), laboratory data (Erythrocyte Sedimentation Rate (ESR) or C-reactive protein (CRP)) and the patient's opinion (Visual Analogue Scale (VAS) for global health) reflects low disease activity if the score is ≤ 2.4. A cut off point of 1.6 has been shown to correspond with the 1981 ACR preliminary criteria for clinical remission, which are less easy to apply.[38,39] Other composite scores have their own cut offs to denote remission. In the hope to create a uniform definition for remission, a joint committee of the ACR, EULAR

Table 2: ACR/EULAR Boolean-based definition of remission in rheumatoid arthritis clinical trials.[40]

At any time point, patient must satisfy all of the following:
Tender joint count ≤ 1
Swollen joint count ≤ 1
C reactive protein (mg/dl) ≤ 1
Patient global assessment (0-10 scale) ≤ 1

and Outcome Measures in Rheumatology (OMERACT) proposed two new definitions for remission in 2011. The first so called 'Boolean based definition' is defined as a tender joint count, swollen joint count, CRP (mg/dl) and VAS global health (1 to 10 scale) all ≤ 1.(table 2) The second definition is defined as a Simplified Disease Activity Index is ≤ 3.3.[40] In chapters 3 and 4 of this thesis we used both the DAS-definition and the Boolean-based definition for remission to calculate remission rates after one year in the Induction therapy with Methotrexate and Prednisone in Rheumatoid Or Very Early arthritic Disease (IMPROVED) study.

The amount of joint damage progression in RA has declined last decades due to more adequate suppression of disease activity by improved treatment strategies. An often used method for assessing radiological damage is the modified Sharp-van der Heijde Score (SHS), in which the amount of erosiveness and joint space narrowing is scored in 44 joints of the hand and feet.[41]

Less has been published about so called 'Patient Reported Outcomes' (PROs), which represent health related quality of life (HRQoL). In RA, pain and functional limitations can cause impairment in social, emotional and psychological functioning, such as anxiety and depressive symptoms.[4] PROs can be disease specific, such as the McMaster Toronto Arthritis questionnaire (MACTAR), or generic such as the Health Assessment Questionnaire (HAQ) and the Short Form (SF)-36. The BeSt study showed that patients with early RA suffer from impaired functional ability and HRQoL compared to the general population, and that current treatment strategies are able to improve, but not normalize HRQoL.[42] In chapter 5 of this thesis the question whether HRQoL measures can be improved more or even be normalized with the proper treatment strategy, will be answered. In chapter 7 we investigate whether patients with early (rheumatoid) arthritis experience symptoms of depression, whether their disease affects their state of optimism and the effect of four months of remission induction therapy on depressive symptoms and optimism scores.[43,44]

UNDIFFERENTIATED ARTHRITIS

If no definitive diagnosis can be made in patients with an inflammatory mono-, oligo- or poly-arthritis, they are said to have undifferentiated arthritis (UA). Over time, this syndrome may naturally evolve into a chronic inflammatory disease or into remission. Several observa-

tional cohorts of early arthritis patients have shown that, depending on the inclusion criteria, 17-32% of the patients progress to RA,[45] while 40-55% achieve spontaneous remission.[46,47] The remaining patients continue to have symptoms of UA or develop other inflammatory diseases. In those patients who over time develop a chronic poly-arthritis, UA can be seen as an early stage of RA.

TREATMENT OF UA

Major improvements achieved by starting treatment soon after RA has been diagnosed, have raised the question whether treating patients even earlier, already in the phase of UA, may be even more beneficial. It has been suggested that, as in other inflammatory diseases such as diabetes type I or Morbus Crohn,[48,49] in an early stage of RA a time period exist in which appropriate treatment may reverse the auto-immune process and alter the disease course. It is hypothesized that intensive treatment in this so called 'window of opportunity' may result in long-term sustained benefits, may prevent RA from becoming a chronic disease and may even cure the disease.[50,51]

To date, only few placebo controlled randomized controlled trials (RCTs) have investigated whether treatment of UA patients is really beneficial. Also, definitions for UA, therapies tested and outcome measures vary considerably among these trials, which impedes making comparisons and drawing conclusions. However, these trials and a number of cohort studies indicate that treating patients in the phase of UA may indeed be advantageous.[52-59] Chapter 2 of this thesis gives an overview of trials a cohort studies, obtained from a systematic literature search on the treatment of UA patients.

The IMPROVED study is the first trial in which both UA and RA patients are included, enabling a head to head comparison of introducing therapy in patients who recently fulfilled the classification criteria for RA with introducing therapy in the phase of UA, when classification criteria are not (yet) met. Data from this trial are used in most parts of this thesis. More details on the IMPROVED study are described below.

THE IMPROVED STUDY

The IMPROVED study, acronym for Induction therapy with Methotrexate and Prednisone in Rheumatoid Or Very Early arthritic Disease, is a multi-centre, randomized, single blinded clinical trial in patients with undifferentiated and early rheumatoid arthritis. The trial was designed by Dutch rheumatologists participating in the Foundation for Applied Rheumatology Research (FARR).

Previously, the PROMPT study had shown that in patients with UA the development of RA could be postponed but not prevented by one year of targeted treatment with MTX monotherapy.[53,60] The BeSt study showed that in patients with early RA a combination of synthetic DMARDs with a tapered high dose of prednisone, earlier investigated in the COBRA trial,[22] was equally effective in suppressing disease activity and radiological damage progression as combination therapy including a biological agent.[16,21] One question that had risen after these trials were done, was whether treating patients earlier, already in the phase of UA, and with combination therapy consisting of MTX and a tapered high dose of prednisone, would improve disease outcomes even more. Because starting treatment this early in disease course could lead to overtreatment of patients who might have achieved spontaneous remission, a second important question was if it would be possible to taper medication as soon as remission was achieved, and if drug free remission (DFR) was an attainable treatment goal. A third essential question was what would be the next best treatment in patients failing on initial combination therapy. Finally, as in the BeSt study and TICORA trial targeting treatment at low disease activity appeared to be very advantageous, [21,61] a last question was if steering at an even more stringent target, namely remission defined as a DAS <1.6, would lead to better disease outcomes.

To address these questions, the IMPROVED study was designed. Patients were treated according to a tight controlled protocol and treatment was steered at remission, defined as a DAS <1.6. As soon as remission was achieved, medication was tapered, if remission was not achieved medication was restarted or intensified. The trial started with an open label

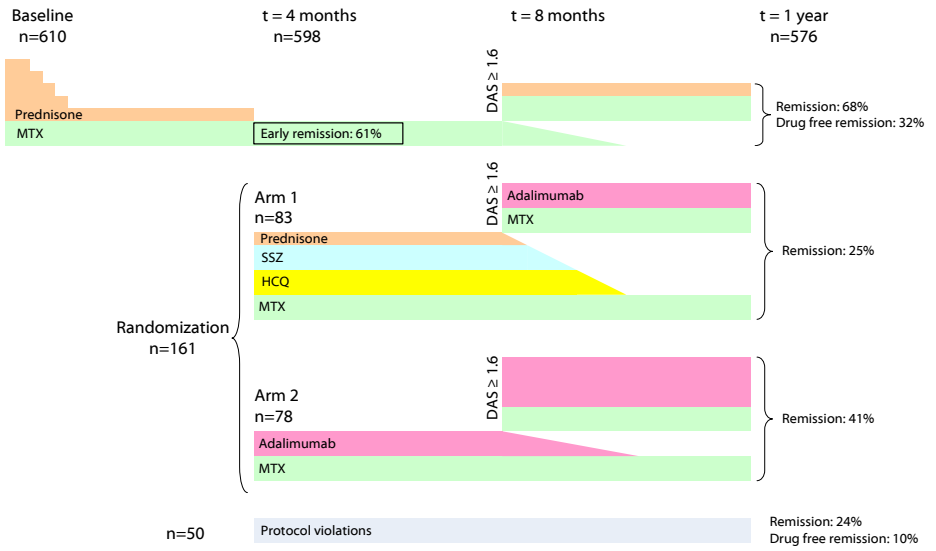

Figure 1: Study flow chart and main results of the first year of the IMPROVED study.
DAS, disease activity score; HCQ, hydroxychloroquine; MTX, methotrexate; n, number; SSZ, sulphasalazine.

remission induction phase, in which all patients were treated with MTX in combination with a high dose of prednisone, tapered in 7 weeks from 60 mg/day to 7.5 mg/day, continued up to 4 months. Patients in remission after 4 months of this initial combination treatment (early remission) started tapering medication, if possible to drug free. Patients not in early remission were randomized to either combination therapy with MTX, sulfasalazine, hydroxychloroquine and low dose prednisone (7.5 mg/day) or to MTX in combination with adalimumab.(figure 1)

Patients were recruited between March 2007 and September 2010 in 12 hospitals in the Western part of the Netherlands. Patients were included if they fulfilled the 1987 criteria for RA with a symptom duration of less than 2 years (RA patients), or if they had at least one arthritic and one other painful joint regardless of symptom duration but not fulfilled the 1987 criteria for RA (UA patients). As in 2010, after inclusion was closed, new classification criteria for RA were proposed,[62] we reclassified all patients according to the new criteria. UA was now defined as having at least one arthritic and one other painful joint but not fulfilling the 2010 criteria for RA.

Primary outcomes are percentages achieved remission (defined as a DAS <1.6) and drug free remission, functional ability (measured by HAQ) and progression of joint damage (assessed by SHS) in UA and RA patients, in patients achieving early remission and in randomized patients, after one, two and five years of follow up. Secondary outcomes were, among others, DAS and PROs such as MACTAR and SF-36.

PREDICTING DISEASE OUTCOME

As we now tend to treat RA patients earlier, already in the stage of UA, and more intensively, we face the risk of overtreatment of those patients who would have achieved remission spontaneously or with a less intensive treatment strategy. Predicting disease outcome in RA, or even better in UA patients, can distinguish patients with a more severe disease course needing progressive treatment strategies from those with less severe disease. Up to now, we can only partly predict disease outcome and there is a need for new predictors to improve existing prediction models.[63-66] A new potential predictor is early metacarpal bone mineral density loss.

BONE LOSS AND DIGITAL X-RAY RADIOGRAMMETRY

The earliest radiological manifestation present in patients with RA is peri-articular bone loss, which has been shown already in the phase of UA and precedes erosions.[67-69] A higher disease activity is associated with more peri-articular bone loss.[70,71] It is hypothesized that inflammatory cytokines such as TNF alpha, IL-1, IL-6 and IL-17 induce bone resorption by stimulating

osteoclasts through up-regulation of receptor activator of nuclear factor κB ligand (RANKL). It is also thought that inflammatory cytokines suppress bone formation by suppressing osteoblast activity through blocking the Wnt pathway by inducing dickkopf-1 (Dkk-1) and sclerostin.[72]

Peri-articular bone loss can be measured in metacarpal bones by Digital X-ray radiogrammetry (DXR). This is a computerised method to estimate metacarpal bone mineral density on digital X-rays of the hands. In the middle three metacarpals, three regions of interest are automatically identified. Per region, multiple measurements contribute to an average cortical thickness and bone width, and from these the final metacarpal bone mineral density (BMD) is calculated.[73]

Metacarpal BMD loss is present in (early) RA and shown to be associated with disease activity.[71,74,75] Also, metacarpal BMD loss after 1 year has previously been shown to be predictive for radiological damage up to five years in patients with RA.[68,76-78]

AIMS AND OUTLINE OF THESIS

This thesis focuses on improving disease outcomes in patients with undifferentiated and early rheumatoid arthritis by new treatment strategies. For all analyses, data from the IMPROVED study were used. Important questions are addressed, such as 'do patients benefit from early treatment, even before they fulfill classification criteria for RA?' and 'is it possible to taper medication as soon as remission is achieved, with the ultimate goal of achieving sustained drug free remission?' and one of the most challenging questions 'can we alter the disease course of RA by early introduction of treatment?'.

Chapter 2 gives an overview of all literature published on drug therapy in patients with undifferentiated arthritis until February 2012. In *chapter 3* main outcomes after 4 months of remission induction therapy in patients with early (rheumatoid) arthritis in the IMPROVED study are given. Both in *chapters 4 and 5* outcomes after one year of early remission steered treatment in the IMPROVED trial are analysed. In chapter 4 primary outcomes and in chapter 5 patient reported outcomes are evaluated. In *chapter 6* determinants of drug free remission are explored in those IMPROVED patients who achieve early remission. *Chapter 7* addresses the questions whether patients with early RA have depressive symptoms, either as a side effect of medication or as response to changes in (symptoms of) disease activity. In *chapter 8* the predictive value of metacarpal bone mineral density loss after 4 months for future joint damage is evaluated. *Chapter 9* describes changes in metacarpal bone mineral density during the first year of remission steered treatment in the IMPROVED study. Finally, an overview and discussion of all results is given in *chapter 10*.

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