Improving disease outcomes in early phases of rheumatoid arthritis

Kirsten Wevers-de Boer

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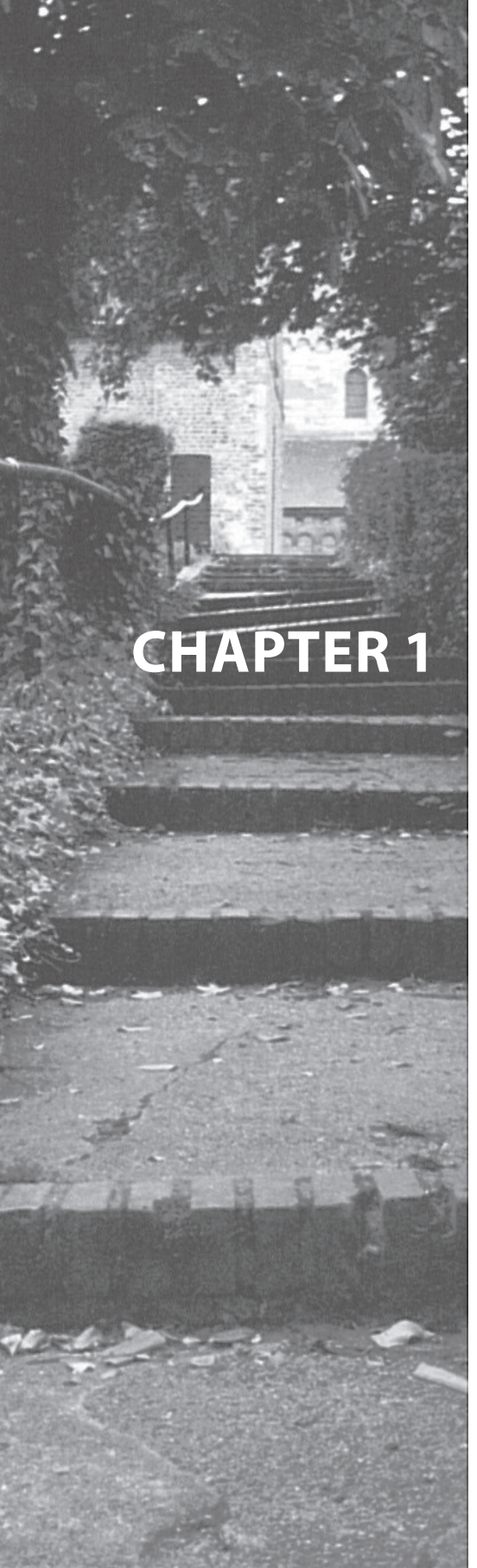

CHAPTER 1 General introduction

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

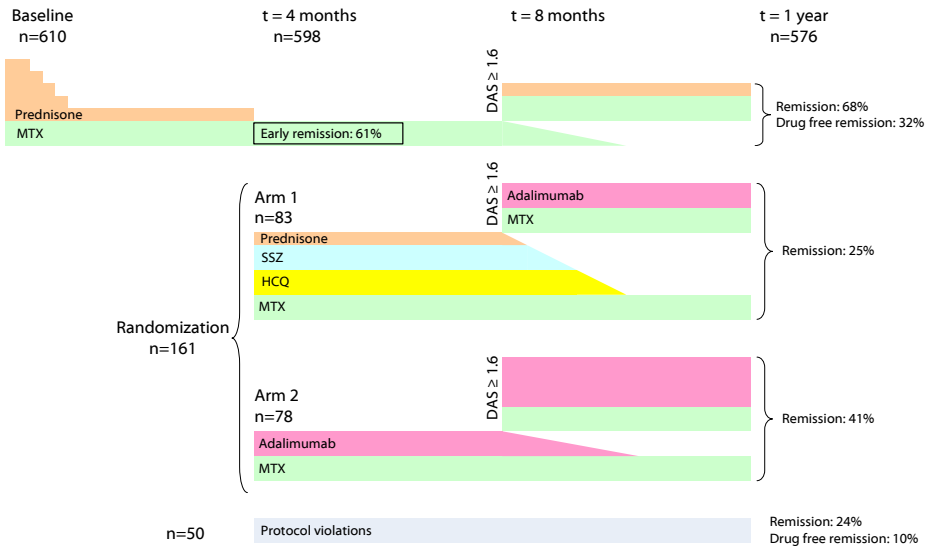

Figure 1: Study flow chart and main results of the first year of the IMPROVED study.
DAS, disease activity score; HCQ, hydroxychloroquine; MTX, methotrexate; n, number; SSZ, sulphasalazine.

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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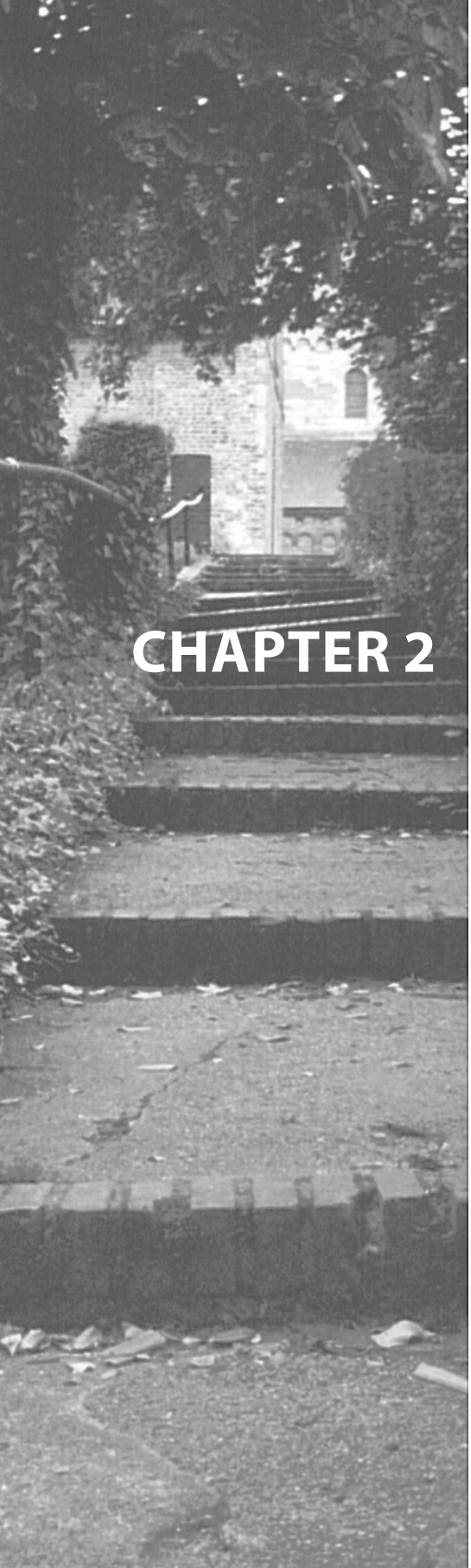

CHAPTER 2

Drug therapy in undifferentiated arthritis: a systematic literature review

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ABSTRACT

Objective

Undifferentiated arthritis (UA) is defined as an inflammatory oligo- or polyarthritis in which no definitive diagnosis can be made. We performed a systematic literature review to assess the efficacy of various drug therapies in patients with UA.

Methods

The systematic literature search was conducted using electronic databases Pubmed, EMBASE and MEDLINE in adults with undifferentiated or early arthritis (not fulfilling the ACR 1987 or ACR/EULAR 2010 criteria for RA). Drug therapy consisted of disease modifying anti-rheumatic drugs (DMARDs), biological agents and oral, intra-muscular (IM) or intra-articular corticosteroids.

Results

Nine publications on 8 randomized controlled trials (RCTs), 2 publications on 2 uncontrolled open-label trials and 7 publications on 3 cohort studies were included. Temporary treatment with methotrexate (MTX), abatacept and IM corticosteroids were demonstrated in RCTs with 12 months to 5 years follow up to be more effective than placebo in suppressing disease activity or radiologic progression. One study suggests that DMARD combination therapy is, at least after 4 months, superior to MTX monotherapy in UA patients at high risk of developing persistent arthritis. The open label uncontrolled trials and cohort studies also suggested that early treatment may provide immediate suppression of inflammation. The long term benefit of early treatment in UA remains unclear.

Conclusions

UA patients benefit from early treatment with MTX. Combining multiple DMARDs or DMARDs with corticosteroids and biological agents may be even more beneficial. However, which treatment may provide the best results or may alter the disease course still has to be determined. More randomized clinical trials with longer follow up time are needed.

INTRODUCTION

Undifferentiated arthritis (UA) is defined as an inflammatory oligo- or polyarthritis in which no definitive diagnosis can be made, and which over time may naturally evolve into a chronic inflammatory disease or into remission. Several observational cohorts of early arthritis patients have shown that, depending on the inclusion criteria, 17-32% of the patients progress to rheumatoid arthritis (RA),[1] while 40-55% achieve spontaneous remission.[2,3]

Since many studies have proven that early treatment of RA improves clinical, functional and radiological outcomes,[4-6] the question has risen if treatment in the stage of UA may be even more beneficial. The so called 'window of opportunity theory' hypothesizes that in an early stage of RA, possibly in the stage of UA, a period may exist in which the disease course can be altered by the appropriate treatment, preventing it from becoming a chronic and disabling disease.[7] In 2010, new classification criteria have been published to enable earlier diagnosis and treatment of RA patients.[8] Recent data have shown that patient indeed are diagnosed earlier,[9] but the benefit of the new criteria in terms of long term disease outcome still needs to be elucidated. Furthermore, also with these new criteria part of the patients with inflammatory oligo- or polyarthritis cannot (yet) be classified as RA.

To investigate whether early initiation of disease modifying anti-rheumatic drugs (DMARDs) is beneficial for patients with UA, we performed a systematic literature review to identify all articles on disease outcomes of drug treatment in patients with UA, and aimed to assess the efficacy of the different drug therapies.

METHODS

The systematic literature search was conducted using electronic databases Pubmed, EMBASE and MEDLINE and restricted to adults with UA or early arthritis (not fulfilling the ACR 1987 or ACR/EULAR 2010 classification criteria for RA). The following definitions were searched for up to February 2012: undifferentiated or early or unclassified or probable (inflammatory) arthritis or oligo- or polyarthritis. Drug treatment was restricted to glucocorticosteroids, DMARDs and biological agents. Articles were only included if they concerned disease outcomes of drug therapy. All types of publications were included and no language restrictions were used.

Using predefined inclusion criteria, titles and abstracts were screened by one researcher and checked up by a second researcher. Disagreements were solved by discussion. Of the selected articles, full texts were screened for final selection in the review. Reference lists of included review articles were hand searched for additional relevant articles. Data extraction was performed by one researcher. Methodological quality of included randomized controlled trials (RCTs) was assessed by two independent researchers following the Guidelines for Cochrane Musculoskeletal Group Systematic Reviews, using the Cochrane Collaboration's

tool for assessing risk of bias.[10] For each study, the risk of several types of bias (selection, performance, detection, attrition and reporting bias and 'other sources of bias') was judged and summarized in an overall risk as low, high or unclear. Also, the Jadad score was performed, a quality score assessing randomization, blinding, withdrawals and drop outs.[11] Scores range from 0-5 with higher scores indicating better methodological quality.

Because of the large heterogeneity in types of patients, drug therapies and outcome measures no meta-analysis was performed.

RESULTS

After screening 3608 titles and abstracts, 67 articles were screened full text.

In total 30 articles were selected: 11 on 10 clinical trials of which 8 were RCTs and 5 placebo controlled, 7 on 3 cohort studies, and 10 review/opinion articles and 2 recommendations which were disregarded for this analysis.(figure 1)

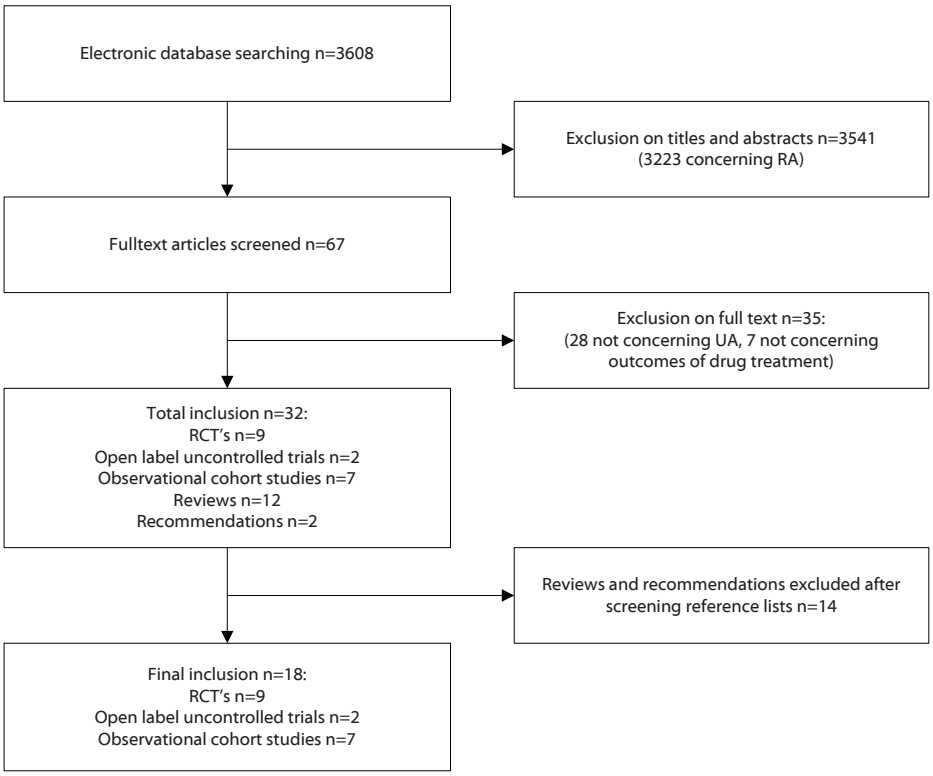

Figure 1: Flow diagram of systematic literature search for publications on drug treatment of patients with undifferentiated arthritis.

Characteristics of clinical trials are shown in table 1. Three trials included both UA and RA patients.[12-14] Drug therapies studied were intra-muscular (IM) or intra-articular (IA) corticosteroids (3 RCTs, 2 placebo controlled, 1 open label trial), DMARDs with or without oral glucocorticoids (GCs) (2 RCTs, 1 placebo controlled, 1 open label trial), biological agents (2 placebo controlled RCTs) and one RCT comparing tight control with 'routine DMARD' treatment. On one placebo controlled RCT two articles with different follow up duration were published.

Characteristics of observational studies are shown in table 2. Five of 7 publications were based on the Norfolk Arthritis Register (NOAR), a primary care-based cohort in adults with ≥2 swollen joints for at least 4 weeks, of which 46% at baseline fulfilled the 1987 criteria for RA.[15] Four studies compared treated and untreated patients and/or early versus delayed start of treatment. Adjustments for differences in disease severity or time dependent confounders between groups were made using propensity scores or marginal structural models (MSM). One publication comparing anti-citrullinated protein antibodies (ACPA) positive and negative patients and two publications without comparisons between treated and/or untreated patients are not further mentioned.

Main outcomes of all included clinical trials are shown in table 3. Seven clinical trials investigated temporary treatment and 3 trials continuous tight controlled treatment. Follow up varied between 3 months and 5 years. Many different outcome measures were used for assessing response to treatment in terms of disease activity state, achieving remission, joint damage or progression to RA.

Results of synthetic DMARDs

Van Dongen et al [16] and van Aken et al [17] compared a 12 months course of methotrexate (MTX) with placebo after 30 months and 5 years follow up. After 30 months 22 (40%) in the MTX group and 29 (53%) in the placebo group had progressed to RA(1987 criteria) (p value not published), after 5 years 25 (45%) and 29 (53%) did (p=0.45). Remission was achieved in comparable numbers after 30 months and 5 years (after 30 months 15 (27%) and 13 (24%) and after 5 years 20 (36%) and 15 (27%) in the MTX and placebo group respectively (p-values not published)). All patients in the placebo group who progressed to RA did so within one year compared to half of the patients in the MTX group (p=0.04), suggesting that progression to RA was at least postponed by one year of MTX treatment. After 30 months, more patients showed radiological progression in the placebo group (14 versus 6, p=0.046), but after 5 years median SHS progression did not differ between groups (p=0.78). Up to 30 months, fewer adverse events (AE) were reported in the placebo group, serious AE (SAE) were reported similarly in both groups.

De Jong et al [14] compared MTX monotherapy with MTX+sulphasalazine (SSZ)+hydroxychloroquine (HCQ) in early arthritis patients at high risk for developing persistent arthritis according to the prediction model of Visser et al.[18] All patients received GC bridging therapy (either a tapering scheme or IM injection). After three months, the combination therapy group

Table 1: Characteristics of clinical trials on drug treatment in patients with early or undifferentiated arthritis.

Study	Year	Type	N	FU	Inclusion criteria	Used definition	Intervention	Primary outcome	Bias risk	Jadad score
Corticosteroid injections										
Green [21]	2001	Open label	51	1 yr	Synovitis ≤5 joints, ≤12 months	'Early oligoarthritis'	Methylprednisolone IA (all arthritic joints)	No clinical synovitis	-	-
Marzo-Ortega [22]	2007	RCT	59	1 yr	Synovitis ≤4 joints, <12 months	'Early oligoarthritis'	Methylprednisolone IA (all arthritic joints) vs NSAIDs, SSZ in case of polyarthritis	Absence of synovitis	High	3
Machold [23]	2010	RCT	389	1 yr	Arthritis ≥1 joints, <16 weeks	'Very early arthritis'	Methylprednisolone IM vs placebo, 1 injection	Clinical remission*	Mod	3
Verstappen [24]	2010	RCT	268	1 yr	Arthritis ≥2 joints, 4-10 weeks	'Early polyarthritis'	Methylprednisone IM vs placebo, 3 injections	Need to start DMARD after 6 months	Low	5
DMARDs										
Van Dongen [16]	2007	RCT	110	30 mo	Probable RA (1958 ACR criteria)	'Probable RA'	MTX vs placebo	Progression to RA, radiological progression	Mod	2
Van Aken [17]	2013	RCT	110	5 yrs	Probable RA (1958 ACR criteria)	'Probable RA'	MTX vs placebo	Progression to RA, radiological progression	Mod	2
De Jong [14]	2012	RCT	281	3 mo	Arthritis ≥2 joints, < 1 year, high likelihood of persistent arthritis	'Early arthritis' (88% RA(2010))	MTX+oralGC vs MTX+SSZ+HCQ +oralGC vs MTX+SSZ+HCQ + IM GC	DAS, HAQ	High	3
Wevers-de Boer [13]	2012	Open label	122	4 mo	≥1 arthritic and ≥1 painful joints, suspect for RA	'Early arthritis' (79% RA(2010))	MTX + tapered high dose prednisone	Remission (DAS<1.6)	-	-
Tight control strategy										
Van Eijk [12]	2012	RCT	82	2 yrs	2-5 swollen joints, <2 years	'Early arthritis' (69% RA(2010))	Remission targeted treatment** vs conventional care	Radiological progression	High	2
Biologicals										
Saleem [19]	2008	RCT	17	6 mo	Arthritis >1 joint, <12 months	'UA'	Infliximab vs placebo	Clinical remission	Mod	2
Emery [20]	2010	RCT	56	18 mo	Arthritis ≤3 criteria of 1987 ACR criteria for RA	'UA'	Abatacept vs placebo	Progression to RA	Mod	4

* clinical remission defined as no swollen joints, <2 tender joints, no treatment other than study drug, 2 of 3 criteria: a) normal C-reactive protein (CRP), b) visual analogue scale (VAS) disease activity <1, c) VAS pain <1

**start with MTX 15 mg, in case of no remission: subsequently switch to MTX + adalimumab, increase adalimumab, switch to MTX+SSZ+HCQ, add prednisone.

DAS, disease activity score; DMARD, disease modifying anti-rheumatic drugs; FU, follow up; GC, Glucocorticosteroids; HAQ, health assesment questionaire; HCQ, hydroxychloroquine; IA, intra-articular; IM, intra-muscular; Jadad score, quality assessment score ranging from 0-5 with higher scores indicating better methodological quality; Mod, moderate; MTX, Methotrexate; N, number of patients; NSAID, non-steroidal anti-inflammatory drugs; RA, rheumatoid arthritis according to the American College of Rheumatology (ACR) 1987 classification criteria; RA(2010), RA according to the ACR/European League Against Rheumatism (EULAR) 2010 classification criteria; RCT, randomized controlled trial; Risk of bias, assessed according to the Cochrane Collaboration's tool for assessing risk of bias; SSZ, Sulfasalazine, UA, undifferentiated arthritis.

Table 2: Characteristics of observational cohort studies in patients with early inflammatory polyarthritis.

Study	Year	N	FU	Inclusion criteria	RA *	ACPA+ *	RF+ *	Comparison	Outcomes	Adj. for severity bias
Wiles [27]	2001	384	5	Swelling ≥2 joints, ≥4 weeks	49%	np	31%	Treatment vs no treatment, early vs delayed treatment	Functional ability	PS
Bukhari [26]	2003	335	5	Swelling ≥2 joints, ≥4 weeks	47%	np	31%	No vs early treatment vs delayed treatment	Radiologic progression	PS
Farragher [15]	2010	642	10	Swelling ≥2 joints, ≥4 weeks	np	np	np	Treatment vs no treatment, early vs delayed treatment	Functional ability	MSM
Lukas [25]	2011	661	1	Arthritis >2 joints, 6 weeks - 6 months, high suspicion for RA	73%	41%	45%	Early vs delayed treatment	Radiologic progression	PS

*at baseline

Three of 7 selected articles on observational cohort studies were not mentioned in this table because no comparisons between early versus delayed treatment were made.

ACPA, anti-citrullinated protein antibodies; Adj, adjustments; DMARD, disease modifying anti-rheumatic drugs; FU, follow up in years; MTX, methotrexate; MSM, marginal structural model; N, number of patients; np, not published; PS, propensity scoring; RA, rheumatoid arthritis according to the 1987 ACR classification criteria; RF, rheumatoid factor; vs, versus.

Table 3: Main outcomes of clinical trials included in the systematic review

Study	Symptom duration (wks)	ACPA+ (%)	RF+ (%)	Female (%)	Age (yrs)	Baseline disease activity		Disease activity response /state		Remission (%)		Joint damage		Progression to RA (%)	Time to prog. to RA
Temporary treatment						**Definition**		**Definition**		**Definition**		**Definition**			
Green [21]	16	NR	22	55	42	*Arthritic joints (median)*	2.3	*No synovitis 12 wks (%)*	45	*ACR1981 52 wks*	18		NR	NR	NR
Marzo-Ortega [22]															
CS IA (1-3 times)	12	NR	6	42	34	*SJC (no.)*	1	*No synovitis 52 wks (%)*	81		NR		NR	NR	NR
Conservative care	10		4	43	31		1		57						
Machold [23]															
CS IM (once)	9	NR	NR	72	48	*Oligo-arthritis (%)*	41	*Persistent remission* 52 wks (%)*	16	*Remission* 12 wks*	22		NR	45	NR
Placebo	8			76	48		36		18		21			51	
Verstappen [24]															
CS IM (3 times)	8	NR	31	68	56	*Mean DAS28(3)*	5.3±1.2	*DAS28(3) 26 wks (mean)*	3.7	*'resolved disease' 52 wks*	**20** #	*Development of erosions 52 wks (%)*	13	49	NR
Placebo	8		35	69	55		5.3±1.2		3.7		**10**		15	60	
Van Dongen [16]															
MTX (12 mo)	45	22	36	64	51	*Mean DAS*	2.7	*Remission 30 mo*	>	*DAS<1.6 30 mo*	27	*SHS progression 30 mo (%)*	**11 †**	40	**HR 1.7‡**
Placebo	38	27	35	69	51		2.5				24		**25**	53	
Van Aken [17]															
MTX (12 mo)	45	22	36	64	51	*Mean DAS*	2.7	*Remission 5 yrs*	>	*DFR DAS<1.6 5 yrs*		*SHS progression 5 yrs (median)*	0 (0-1)	45	**100¶**
Placebo	38	27	35	69	51		2.5						0 (0-1)	53	**44**
Saleem [19] **															
Infliximab (14 wks)	32	8/10	7/10	8/10	51	*Mean DAS28*	5.3	*Remission 26 wks*	>	*No synovitis CRP<10 26 wks*	2/10		NR	10/10	26 wks
Placebo	36	4/7	3/7	6/10	58		4.3				1/7			5/7	14 wks
Emery [20]															
Abatacept (6 mo)	35	NR	86	71	45	*Mean DAS28 (CRP)*	3.6	*Remission 52 wks*	>	*DAS28(CRP) <2.6 52 wks*	47	*Difference in G-mS TS 52 wks*	**-1.1††**	46	NR
Placebo	28		71	71	45		3.4				39		ref	67	

Table 3: Main outcomes of clinical trials included in the systematic review (Continued)

Study	Symptom duration (wks)	ACPA+ (%)	RF+ (%)	Female (%)	Age (yrs)	Baseline disease activity		Disease activity response /state		Remission (%)		Joint damage		Progression to RA (%)	Time to prog. to RA
Continuous treatment						**Definition**		**Definition**		**Definition**		**Definition**			
Van Eijk [12]															
Tight Control	24	60	48	58	48	*Mean DAS*	2.2±0.5	*Mean DAS*	1.4	*DAS*	66	*Median*	0	NR	NR
Conventional care	24	60	33	79	46		2.4±0.7	*2 yrs*	1.7	*<1.6*	49	*increase SHS*	0.25		
										2 yrs		*2 yrs*			
De Jong [14]															
MTX	22	58	53	70	54	*Mean DAS*	3.4±1.0	*Difference in*	ref	*DAS<1.6*	31		NR	NR	NR
Mutiple DMARDS	25	59	58	66	54		3.3±1.0	*mean DAS*	**-0.4 ‡‡**	*3 mo*	44				
								3mo							
Wevers-de Boer [13]															
RA	18	68	69	70	52	*Mean DAS*	3.3±0.9	*Mean DAS*	1.5	*DAS<1.6*	61	*Median SHS*	0	NR	NR
UA	16	3	4	61	52		2.7±0.7	*4 mo*	1.4	*4 mo*	65	*progression*	0		
												4 mo			

* clinical remission defined as no swollen joints, <2 tender joints, no treatment other than study drug, 2 of 3 criteria: a) normal CRP, b) VAS disease activity<1, c) VAS pain<1

** because of small number of study participants, for this study no./total was presented instead of percentages.

Significant differences are pressed bold

OR 0.42 (0.18-0.99), p=0.048

† p=0.046

‡ p=0.04

†† 95% CI (-2.1; -0.2)

‡‡ 95% CI (-0.7; -0.1)

¶ % progression to RA within 1 year; Kaplan Meier Survival analysis after 5 years: MTX versus placebo p=0.11, ACPA positive patients versus ACPA negative patients: p<0.001

ACPA, anti-citrullinated protein antibodies; ACR1981: preliminary criteria for clinical remission in RA, ACR 1981; CRP, C-reactive protein; CS, corticosteroids; DAS, original disease activity score; DAS28, disease activity score based on 28 joint count; DAS28(3), DAS28 3 components; DFR, drug free remission; G-mS TS, Genant modified Sharp total score; IA, intra-articular; IM, intra-muscular; mo, months; NR, not reported; RF, rheumatoid factor; ref, reference; SJC, swollen joint count; wks, weeks; yrs, years.

had a lower mean Disease Activity Score (DAS) than the monotherapy group (difference (95% CI) 0.39 (0.67-0.11)). No significant difference was seen between oral and IM GC bridging therapy. AE and SAE were reported in 67 (75%) and 50 (56%) in the combination therapy and the monotherapy group. Fewer medication changes were made in the monotherapy group (14 (16%) versus 18 (20%), p=0.006).

In an open label trial in patients with UA or recent onset RA(2010 criteria),[13] MTX was combined with a tapered high dose of prednisone for 4 months. Remission after 4 months was achieved in 79 (65%) UA and 291 (61%) RA patients (p=0.5). Median (IQR) SHS progression was 0 (0-0) in both UA and RA patients (p=0.9). AE were reported in 341 (56%) and SAE in 16 (3%) of all patients.

These studies indicate that synthetic DMARDs suppress disease activity in UA patients. MTX monotherapy may postpone but not prevent the development of RA and may slow down radiological progression. It appears that initial combination therapy with MTX and multiple DMARDs or corticosteroids (oral or parenteral) results in better short term clinical outcomes. No long term data are available.

Results of biological DMARDs

Two trials have investigated biological agents in UA patients. Saleem et al [19] compared a 14 week course of infliximab with placebo in UA patients who had relapsed after a single corticosteroid injection. If clinical inflammation was persistent after week 14, MTX was started. Independent safety monitors halted recruitment 'because of poor outcomes in all subjects' before inclusion was completed, after inclusion of 17 patients (10 randomized to infliximab, 7 to placebo) Clinical remission at 26 weeks was achieved in 1 patient and 2 patients in the placebo and infliximab group respectively. After 1 year, all patients in the infliximab group had progressed to RA (1987 criteria) compared to 5/7 in the placebo group, in which this occurred earlier (after a median of 14 compared with 26 weeks, respectively). Data on (S)AE were not reported.

Emery et al [20] compared a six months course of abatacept with placebo. After 1 year, respectively 12 (46%) and 16 (67%) of the abatacept and placebo group progressed to RA(1987 criteria) (difference (95% CI) -21% (-47% to 8%)). Radiologic progression (Genant-modified Sharp score) after one year was significantly less in the abatacept group (difference in total score -1.10 (95% CI -2.05 to -0.15)). Remission (DAS28 definition) after 1 year was achieved in 9 (47%) and 5 (39%) in the abatacept and placebo group respectively. Numbers of reported AE and SAE were similar.

These trials suggest that a biological agent may slow down progression to RA in UA patients. Early treatment with abatacept appears to suppress radiological damage progression. Long term benefits remain uncertain.

Results of corticosteroid injections

Green at al [21] performed an open label pilot with IA GC injections in all arthritic joints in 51 patients. Clinical synovitis was absent in 23 (45%) and 26 (51%) after 12 weeks one year respectively.

Marzo-Ortega et al [22] injected all inflamed joints with GC (early intervention (EI) group) and compared this with 'conservative treatment' (CT group) with a nonsteroidal anti-inflammatory drugs (NSAID). In case of progression to polyarthritis SSZ was started. Clinical synovitis was absent in 25 (81%) and 16 (57%) patients after 52 weeks in the EI and CT group respectively (p=0.05), but more patients in the EI group started DMARD treatment (14 (45%) versus 4 (14%), p=0.012). The EI group reported a significantly lower mean Visual Analogue Scale (VAS) pain after 4 weeks than the CT group, but not after 12 and 52 weeks. Data on (serious) AE were not reported.

Machold et al [23] compared a single IM injection of GC with placebo. Respectively 32 (16%) and 33 (18%) in the GC and placebo group achieved persistent remission without additional treatment after 1 year (p=0.68). Initiation of a DMARD and core set variables were comparable. AE generally were mild and comparable between groups.

Verstappen et al [24] compared a three week course of IM GC injections with placebo. When patients met ≥2 of 4 predefined criteria (≥3 swollen joints, ≥6 painful joints, morning stiffness ≥45 minutes or erythrocyte sedimentation rate ≥28 mm/h), they were referred for DMARD treatment. After 6 months, patients in the placebo group were more often referred for DMARD treatment than the GC group (96 (76%) versus 77 (61%), adjusted OR (95% CI) 2.11 (1.16-3.85), p=0.015). After 1 year, remission without DMARD use was less often achieved in the placebo group (11 (10%) versus 22 (20%), adjusted OR (95% CI) 0.42 (0.18-0.99), p=0.048). Sixty seven (60%) and 54 (49%) in the placebo and GC group were classified as RA(1987 criteria) (adjusted OR (95% CI) 1.58 (0.85-2.93), p=0.15). AE were comparable between groups.

These studies indicate that a single corticosteroid injection probably has no long term benefit. Repeated IM corticosteroid injections may postpone the need to start DMARDs but not prevent progression to RA, and in one study possibly encourage remission. No long term follow up data exist.

Results of tight control and treat to target strategies

Van Eijk et al [12] compared tight control treatment (TC group) with conventional care (CC group) in early arthritis patients. The TC group (n=42) started with MTX monotherapy, medication was intensified in case of no remission (19 patients changed to adalimumab, 15 increased adalimumab, 11 switched to multiple DMARDs , 3 added prednisone and 1 switched to leflunomide). The CC group (n=40) used conventional DMARDs without treatment target (24, 14 and two patients started HCQ, MTX and SSZ respectively). No prednisone or biologics were allowed. After 2 years, respectively 66% and 49% in the TC and CC group were in remission (numbers and p-value not published). Median SHS progression was 0 (0-1.0) and 0.25 (0-2.5)

in the TC and CC group (p=0.17). Over two years, no significant differences in DAS and Health Assessment Questionnaire (HAQ) levels were seen. The number of reported AE was higher in the TC group (62 versus 35, p=0.03). The number of SAE was comparable.

In conclusion, this trial shows no benefit to patients with UA of tight control treatment over conventional care in terms of radiological and clinical outcomes and achieving remission.

Early versus delayed treatment

No RCTs compared early versus delayed start of treatment in patients with UA. In an open label study [13] no difference in proportions remission was found between UA and RA (2010 criteria) patients after a four months of MTX and a tapered high dose of prednisone. But although UA patients had a lower baseline DAS, baseline symptom duration was similar between UA and RA patients.

In an observational study in the ESPOIR cohort, Lukas et al [25] compared early versus delayed treatment, adjusted for selection bias using propensity scores. The estimated marginal mean (SE) SHS progression was 0.8 (0.37) and 1.7 (0.19) in patients who respectively started DMARD therapy within and after 3 months (p=0.03). Stratification in propensity quintiles showed that only patients with high baseline disease activity starting DMARD therapy after 3 months showed more progression than patients starting within 3 months.

Bukhari et al [26] found a similar result in the NOAR cohort, also using propensity scores. Starting treatment within 6 months after symptom onset was associated with less radiologic damage after 5 years than starting after 6-12 months and >12 months (OR (95% CI) 1.5 (0.9-2.3) versus 2.3 (1.4-3.9) and 2.2 (1.4-3.5) respectively, with untreated patients as reference (1.0)).

Wiles et al [27] compared early versus delayed treatment in the NOAR cohort using propensity scores, with functional ability after 5 years as outcome. Starting treatment early (within 6 months of symptom onset) was not associated with a HAQ score ≥1.0 (OR 0.71 (0.34 to 1.44), but starting treatment after 6-12 and >12 months was (OR (95% CI) 1.98 (0.86 to 4.54) and 2.03 (1.10-3.75) respectively, with untreated patients as reference (1.0)). Farragher et al [15] used functional ability after 10 years as outcome and adjusted for time dependent confounders using MSM. Patients treated within 6 months after symptom onset improved more in functional ability than untreated patients, although not significantly (difference (95% CI) in change from baseline HAQ -0.24 (-0.58-0.09)). In patients treated after 6-12 months and >12 months functional ability improved less than in untreated patients (difference (95% CI) in change from baseline of respectively 0.12 (-0.13;0.37) and 0.18 (-0.06;0.41)). For each month that treatment was started earlier within 6 months, a significant additional benefit was found (difference (95% CI) in change from baseline HAQ -0.10 (-0.19 to -0.02) per month).

In conclusion, results from these observational cohort studies may indicate that disease outcomes improve if treatment is started within at the most six months after symptom onset, and starting sooner may even be better.

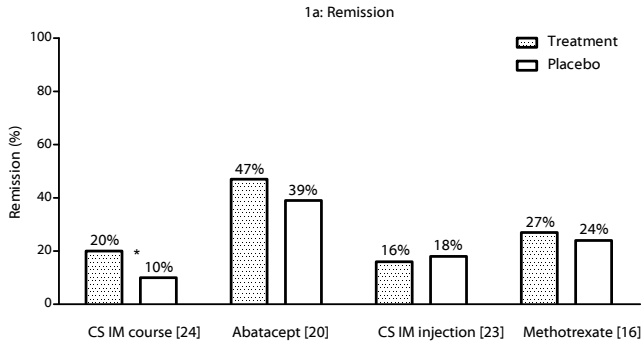

Figure 2a: Remission percentages after one year [24,20,23] and 30 months [16] follow up of the four completed placebo controlled trials on temporary treatment of patients with undifferentiated arthritis * significant difference.

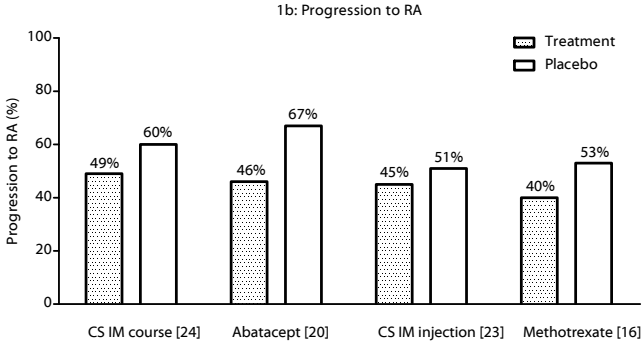

Figure 2b: Percentages of patients who progressed to rheumatoid arthritis after one year [24,20,23] and 30 months [16] follow up of the four completed placebo controlled trials on temporary treatment of patients with undifferentiated arthritis.

DISCUSSION

This systematic literature review shows that to date, few placebo controlled RCTs have been done to answer the question if early treatment in patients with undifferentiated arthritis is beneficial and which treatment might be the best. To compare results is difficult because of inconsistent outcome measures. Five clinical trials, two open label studies and four observational studies suggest that starting treatment early may provide symptom relief, improve functional ability and suppress radiological progression. It may also postpone progression to classifiable RA or the need for other therapies. The strongest evidence of a potential benefit is present on early treatment with MTX, possibly in combination with other DMARDs or corti-

costeroids. Observational studies, which by using propensity scoring and minimal structural models try to partially compensate for indication bias, suggest that other DMARDs than MTX may be used. Data from these cohorts also suggest that starting treatment in UA may be a case of 'the earlier the better'. The benefit of earlier treatment has been previously demonstrated for patients with RA.[4,5,28,29] But contrary to what is recognized and recommended for patients with classifiable RA,[30,31] one study suggests that patients with UA may not gain additional benefit from tight controlled targeted treatment.[12]

The ultimate goals in the treatment of UA would be to prevent progression to destructive RA or even induce permanent remission. Achieving these goals would mean that the so called 'window of opportunity', in which appropriate treatment can alter the disease course, does exist. The closest evidence for the presence of the window of opportunity possibly comes from a study in 253 UA patients,[24] where after a three week course of IM corticosteroid injections more patients achieved remission (20% versus 10%), fewer required initiation of DMARDs (61% versus 76%) and possibly fewer progressed to classifiable RA than in the placebo group (49% versus 60%). Also 6 months abatacept appears to suppress progression to RA, at least over 1 year follow up, although no statistically significant difference was found possibly due to small numbers.[20] Similarly, a one year course of MTX suppressed progression to RA and radiological progression, but after discontinuation of MTX the disease appeared to rerun its course.[16,17] None of the articles included data on sustained drug free remission.

Over diagnosing as 'early RA' followed by overtreatment is a serious concern when treating patients with UA, or even patients who according to the new 2010 criteria would now be classified as RA. Patients may have another illness that may go into spontaneous remission. The solution may lay in predicting disease outcome, such as persistent arthritis or radiologic progression, or response to treatment. Prediction models for disease outcome have been developed.[18,32] However, to predict disease outcome and response to treatment in individual patients is not yet possible.

In conclusion, there are limited trials and observational studies exploring the possibility of inducing remission and/or permanently altering the disease course in UA patients. Long term follow up data are mostly not available. During treatment with MTX monotherapy, combination therapy with multiple DMARDs or corticosteroids, biological agents and intra-muscular corticosteroid injections, active inflammation and ensuing radiographic damage may be suppressed. Early initiation of treatment may be better than delayed initiation, in particular if disease activity appears to be high. Thus, we should optimize strategies for early referral and early identification of patients with arthritis. In addition, any new randomized clinical trials in UA patients should include a short term placebo arm to investigate if early treatment can induce (drug free) remission and a long term follow up period to demonstrate if early treatment can alter the disease course.

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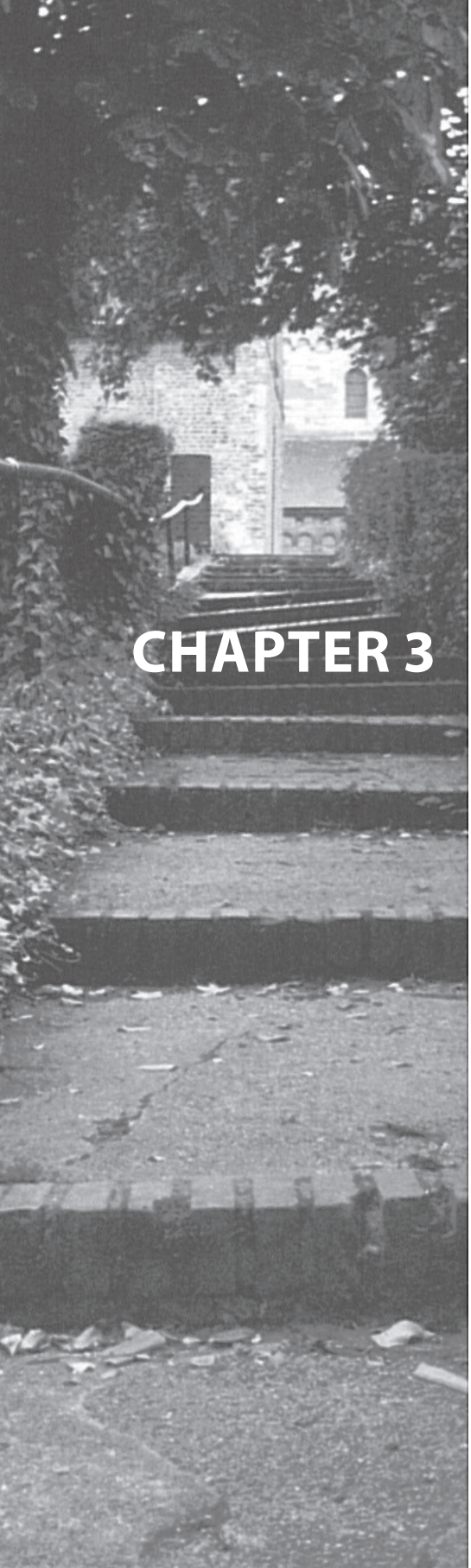

CHAPTER 3

Remission Induction Therapy with Methotrexate and Prednisone in patients with Early Rheumatoid and Undifferentiated Arthritis (the IMPROVED study)

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ABSTRACT

Objective

Classifying more patients as rheumatoid arthritis (2010 ACR/EULAR criteria for RA) may improve treatment outcomes but may cause overtreatment in daily practice. We determined the efficacy of initial methotrexate (MTX) plus prednisone treatment in patients with 1987 or 2010 classified RA and undifferentiated arthritis (UA).

Methods

Six-hundred-ten patients with recent onset RA or UA started with MTX 25 mg/week and prednisone 60 mg/day tapered to 7.5 mg/day in 7 weeks. Percentages remission after 4 months were compared between RA (1987 or 2010 criteria) and UA. Predictors for remission were identified.

Results

With the 2010 criteria 19% more patients were classified as RA than with the 1987 criteria, but similar remission rates were achieved: 291/479 (61%) 2010 classified RA and 211/365 (58%) 1987 classified RA patients ($p=0.52$), and 79/122 (65%) UA ($p=0.46$). ACPA positive RA patients achieved more remission (66%) than ACPA negative RA patients (51%, $p=0.001$), but also had a lower mean baseline DAS (3.2 versus 3.6, $p<0.001$). ACPA negative RA patients who achieved remission had a shorter median symptom duration. Independent predictors for remission were male sex, low joint counts, DAS and HAQ, low Body Mass Index (BMI) and ACPA positivity.

Conclusions

Initial treatment with MTX and a tapered high dose of prednisone results in similarly high remission percentages after four months (about 60%) in RA patients, regardless of fulfilling the 1987 or 2010 criteria, and UA patients. Independent predictors indicate that initiating treatment while disease activity is relatively low results in more remission.

INTRODUCTION

Starting treatment earlier in the disease course of Rheumatoid Arthritis (RA) has improved functional and radiological outcome as compared to delayed treatment.[1-6] New RA classification criteria support this trend,[7] but have triggered concerns that some patients may now be misclassified and overtreated as a result.[8]

Remission has increasingly become a treatment goal in clinical trials, resulting in remission rates that vary between 26% and 42%.[9]

It is hypothesized that starting treatment already in the phase of Undifferentiated Arthritis (UA) may prevent progression to classified RA and increase permanent remission rates. However, methotrexate (MTX) monotherapy for patients with probable RA postponed but did not prevent progression to RA. Similar drug free remission rates (about 25%) were achieved in the MTX group and the placebo group.[10]

Since in RA initial combination treatment with prednisone leads to a more rapid clinical improvement and less radiological progression of joint damage than disease modifying anti-rheumatic drugs (DMARD) monotherapy,[3,11-14] treatment with combination possibly in the phase of UA may increase remission and drug free remission rates, as well as improve short-term functional outcome and long-term joint damage progression.

To investigate this, we designed the IMPROVED (Induction therapy with Methotrexate and Prednisone in Rheumatoid Or Very Early arthritic Disease) study, the first clinical trial in patients with UA and early RA, with an induction phase with MTX and a tapered high dose of prednisone, aimed at achieving remission. This trial allowed us to evaluate the effect of classifying patient groups according to the old and the new RA classification criteria and to identify predictors of remission.

METHODS

Study design

The IMPROVED-study is a multicenter, clinical trial in recent onset RA and UA patients. All patients were initially treated for four months with MTX 25 mg/week and a tapered high dose of prednisone, starting with 60 mg/day, tapered in 7 weeks to 7.5 mg/day, continued in this dose up to four months. Later, this introduction phase will be followed by a single blind randomized controlled trial, where those patients who did not achieve remission will be treated according to two treatment strategies; one starting with a combination of MTX, sulfasalazine, hydroxychloroquine and low dose prednisone, the other with a combination of MTX with adalimumab.

Rheumatologists participating in the Foundation for Applied Rheumatology Research (FARR) designed and conducted the study. Patients were recruited between March 2007 and

September 2010 in 12 hospitals in the Western part of the Netherlands. The Medical Ethics Committee of each participating centre approved the study protocol and all patients gave written informed consent. The IMPROVED trial was registered in the ISRCTN Register (number 11916566) and the EudraCT (number 2006-006186-16).

Patients

Patients with RA classified according to the 1987 American College of Rheumatology (ACR) criteria [15] with a symptom duration of < 2 years and UA, defined as likely to have early RA according to the treating rheumatologist, with at least one arthritic joint and one other painful joint, regardless of symptom duration, were included in the trial. All patients had a disease activity score (DAS) ≥1.6.[16]

Exclusion criteria included previous therapy with DMARDs or corticosteroids, pregnancy or pregnancy wish during the study, malignancy within the last five years, bone marrow hypoplasia, elevated liver enzyme levels (alanine transaminase (AST) and/or aspartate transaminase (ALT) >3 times normal value), serum creatinine level >150 umol/l or estimated creatinine clearance of <75%, uncontrolled diabetes mellitus, uncontrolled hypertension, heart failure (NYHA class III/IV), alcohol or drug abuse, serious infections in the previous 3 months or chronic infectious disease, opportunistic infections within previous 2 months, active or latent hepatitis B infection, documented HIV infection or AIDS, lymphoproliferative disease and multiple sclerosis. All patients with active tuberculosis (TB) were excluded, as well as UA patients with latent TB. RA patients with latent TB could be included if they started adequate anti-tuberculous therapy (according to local TB specialists) prior to initiation of high dose prednisone.

Reclassification according to the 2010 ACR/EULAR classification criteria

After inclusion was complete the new classification criteria were published. Unless specified otherwise (by adding the year of classification criteria between brackets), 'RA' in the text denotes RA classified according to the 2010 criteria, and 'UA' denotes not fulfilling the 2010 criteria.

Outcomes

Primary outcomes after four months were percentage clinical remission, defined as a DAS <1.6,[16] disease activity measured by DAS, functional ability measured by the Health Assessment Questionnaire (HAQ)[17] and radiological progression using the Sharp/van der Heijde scoring method (SHS).[18]

Radiological damage was assessed by two independent readers using SHS, blinded for patient identity and time order of the radiographs.[18] Progression was defined as an increase in SHS score of ≥0.5 points. Due to the small distribution of SHS scores, caused by a large proportion of patients without progression, the inter-observer and intra-observer intraclass

correlation coefficients (ICC) were not suitable for measuring reliability.[19] In 91.5% of patients both readers scored the same progression. In the others, the median (IQR) difference in progression score between readers was 2 (2-3). A consensus score was reached for radiographs with inter-reader differences ≥ median difference in progression score (n=41).

Percentages remission according to ACR/EULAR preliminary definition [20] were compared with percentages remission based on the DAS.

Statistical analysis

All outcomes were calculated according to the intention-to-treat (ITT) principle. Percentages remission in the RA and the UA group were compared using Chi-square test. Categorical variables were compared between groups using Chi-square test, normally distributed outcome measures using Independent Samples t-test and skewed outcome measures using Mann-Whitney U-test.

Independent predictors for remission were identified using univariate followed by multivariate logistic regression with achieving or not achieving remission as binominal dependent variable. All available clinical variables were entered in a univariate regression analysis. Using a P-value <0.10, significant variables were then entered in the multivariate regression analysis.

RESULTS

Study profile

Between March, 2007 and September, 2010, 730 patients signed informed consent and were screened for inclusion.(figure 1) We included 610 patients; 364 RA patients (1987 classification criteria) or 479 RA patients (2010 classification criteria) and 122 UA patients (i.e. not fulfilling the 2010 classification criteria).(table 1)

During 4 months 12 patients left the trial: 2 patients because of a revised diagnosis (1 osteoarthritis, 1 lupus), 2 because of comorbidity, 6 withdrew consent and 2 died.(figure 1)

Table 1: Classification of patients according to the 1987 ACR and the 2010 ACR/EULAR criteria for RA.

Inclusion 1987 criteria, no (%)	RA (1987): 364 (60%)	UA: 246 (40%)
Reclassification 2010 criteria, no (%)*	RA (2010): 479 (79%)	UA (2010): 122 (20%)
	RA (2010)	UA (2010)
RA (1987), no (%)	324/364 (89%)	34/364 (9%)
UA, no (%)	155/246 (63%)	88/246 (36%)

*9 patients could not be classified because of insufficient data.
no, number; RA (1987), RA according to the 1987 classification criteria for RA; UA, at least one swollen and one painful joint, at risk for developing RA according to the rheumatologist; RA (2010), included in trial as RA (1987) or UA, reclassified as RA according to the 2010 classification criteria for RA; UA (2010), included in trial as RA (1987) or UA, not fulfilling the 2010 classification criteria for RA.

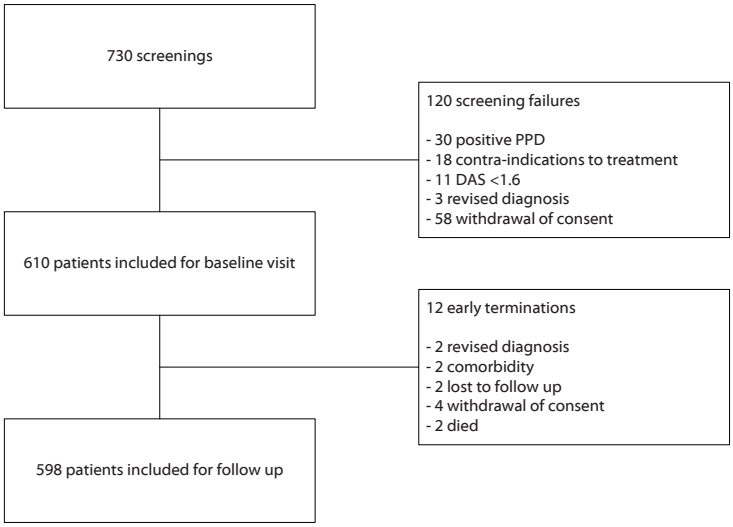

Figure 1: Flow chart of screenings failure and early terminations
PPD, purified protein derivative; DAS, disease activity score.

Baseline characteristics

RA (1987) patients had a higher mean DAS based on more affected joints, higher erythrocyte sedimentation rate (ESR) and higher serum C-reactive protein (CRP) than RA (2010) patients. UA patients included fewer females, were less often RF and ACPA positive, had lower disease activity and HAQ. There was no significant difference between RA (1987 or 2010 classified) and UA patients in baseline damage scores or erosiveness.(table 2)

After four months, DAS <1.6 was achieved in 58% of the RA (1987), 61% of the RA (2010) (p=0.52) and 65% of the UA patients (p=0.46 compared to RA 2010).

DAS improved more in the RA (2010) group than in the UA group and similar as in the RA (1987) group, resulting in comparable mean (SD) DAS levels after 4 months: 1.4 (0.9) in UA, 1.6 (0.9) in RA (1987) and 1.5 (0.9) in RA (2010) patients. Also HAQ improved more in the RA patients than the UA patients, resulting in HAQ levels of 0.44 both in UA and RA patients (p=0.96) after 4 months.

Baseline and 4 months radiographs of hands and feet were available for 546 patients. After four months, 61 patients (10%) showed radiological progression, without a difference between UA and RA patients. In those with progression the median (IQR) SHS progression was 1(1-1) points.

Patients who did not achieve remission after 4 months treatment had a higher baseline DAS, and higher DAS components, and were more often ACPA negative than patients who did achieve remission (table 3). Of the ACPA positive RA patients, 66% achieved remission compared to 51% of the ACPA negative RA patients (p=0.001). ACPA positive RA patients had

Table 2: Baseline characteristics and clinical outcomes after 4 months of patients classified as rheumatoid arthritis either by 1987 or 2010 criteria and of patients with undifferentiated arthritis.

	RA (1987)	**RA (2010)**		**UA**	
Baseline	N= 364	N= 479	P-value	N= 122	P-value*
Age, years (mean, SD)	53.5 (14)	52 (13)	0.08	52 (16)	0.90
Female, no (%)	256 (70)	333 (70)	0.8	74 (61)	0.06
Symptom duration, weeks (median, IQR)	17 (8-32)	18 (9-34)	0.25	16 (8-28)	0.14
RF positive, no (%)	245 (67)	330 (69)	0.59	5 (4)	<0.001
ACPA positive, no (%)	228 (63)	324 (68)	0.15	4 (3)	<0.001
ESR mm/hr (median, IQR)	29 (15-45)	26 (12-41)	0.04	16 (9-38)	0.01
CRP mg/l (median, IQR)	13 (6-35.5)	11 (5-28)	0.046	10 (4-24)	0.25
DAS (mean, SD)	3.50 (0.9)	3.34 (0.9)	0.02	2.70 (0.65)	<0.001
Swollen Joint Count (median, IQR)	8 (4-12)	7 (3-11)	0.02	3 (2-6)	<0.001
Tender Joint Count (median, IQR)	7 (5-11)	7 (4-10)	0.18	5 (3-8)	<0.001
HAQ (mean, SD)	1.26 (0.65)	1.19 (0.67)	0.11	1.03 (0.62)	0.02
BMI (mean, SD)	25.5 (4.1)	25.9 (4.5)	0.18	25.8 (4.0)	0.88
Total SHS (median, IQR)	0 (0-1)	0 (0-0.5)	0.33	0 (0-0.4)	0.98
Erosive, no (%)	49 (13)	60 (13)	0.62	12 (9)	0.46
4 months follow up					
DAS (mean, SD)	1.56 (0.89)	1.52 (0.89)	0.56	1.43 (0.85)	0.30
HAQ (mean, SD)	0.45 (0.51)	0.44 (0.53)	0.81	0.44 (0.51)	0.96
Improvement DAS (mean, SD)	1.93 (1.04)	1.82 (1.04)	0.11	1.26 (0.88)	<0.001
Improvement HAQ (mean, SD)	0.80 (0.64)	0.74 (0.66)	0.16	0.59 (0.61)	0.03
Total SHS (median, IQR)	0 (0-1)	0 (0-0.5)	0.37	0 (0-0)	0.85
Erosive, no (%)	48 (13)	64 (13)	0.98	11 (9)	0.22
SHS progression (median, IQR)	0 (0-0)	0 (0-0)	0.75	0 (0-0)	0.93
Remission (DAS <1.6), no (%)	211 (58)	291 (61)	0.52	79 (65)	0.46

* P-value based on difference between RA (2010) and UA (2010)

ACPA, anti-citrullinated protein antibodies; BMI, body mass index; CRP, C-reactive protein; DAS, disease activity score; erosive, defined as having ≥1 erosions; ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire; IQR, inter quartile range; no, number; RA (1987), RA according to the 1987 classification criteria for RA; RA (2010), RA according to the 2010 classification criteria for RA; RF, rheumatoid factor; SD, standard deviation; SHS, Sharp-van der Heijde Score; UA, undifferentiated arthritis.

a lower baseline DAS (mean (SD) 3.19 (0.89)) than ACPA negative RA patients (mean (SD) 3.64 (0.94), p<0.001). ACPA negative RA patients who achieved remission had a shorter median (IQR) symptom duration (12 weeks (8-26)) than those who did not (20 weeks (10-31), p=0.02). In the whole study population, there was a trend for more remission in patients with shorter symptom duration.

The distribution of joints was different in patients with RA and UA. All RA patients had involvement of small joints (wrists, hands and feet), compared to 94% of the UA patients

Table 3: Baseline characteristics and clinical characteristics after 4 months of patients achieving remission versus patients not achieving remission.

	Remission	**No remission**	
Baseline	N=375	N=221	P-value
DAS (mean, SD)	2.99 (0.85)	3.57 (0.92)	<0.001
Swollen joint count	5 (2-9)	7 (3-12)	0.001
Tender joint count	5 (3-8)	8 (6-14)	<0.001
VAS global health, mm (mean, SD)	42 (24)	52 (21)	<0.001
ESR mm/hr (median, IQR)	23 (10-38)	25 (13-41)	0.20
HAQ (mean, SD)	1.03 (0.65)	1.37 (0.62)	<0.001
Small joints* (median, IQR)	8 (4-13)	12 (7-18)	<0.001
Large joints** (median, IQR)	1 (0-2)	2 (1-4)	<0.001
Age, years (mean, SD)	52 (14)	51 (14)	0.54
Symptom duration, weeks (median, IQR)	16 (9-30)	21 (9-37)	0.08
Female no (%)	231 (62)	172 (78)	<0.001
RF positive no (%)	219 (58)	111 (50)	0.09
ACPA positive no (%)	220 (59)	106 (48)	0.007
Diagnosis RA(2010) no (%)	291 (78)	177 (80)	0.46
BMI	25.4 (3.9)	26.6 (5.1)	0.001
4 months follow up			
DAS (mean, SD)	0.94 (0.36)	2.45 (0.65)	<0.001
Swollen joint count	0 (0-0)	1 (0-4)	<0.001
Tender joint count	0 (0-1)	4 (3-8)	<0.001
VAS global health, mm (mean, SD)	13 (14)	36 (21)	<0.001
ESR mm/hr (median, IQR)	6 (3-13)	11 (6-22)	<0.001
HAQ (mean, SD)	0.23 (0.33)	0.82 (0.59)	<0.001

*number of swollen and/or tender small joints (metacarpophalangeal joints, proximal interphalangeal joints, thumb interphalangeal joints, wrists, second through fifth metacarpophalangeal joints)
** number of swollen and/or tender large joints (shoulders, elbows, hips, knees, ankles)
ACPA, anti-citrullinated protein antibodies; BMI, body mass index; DAS, disease activity score; ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire; IQR, inter quartile range; no, number; RF, rheumatoid factor; RA (2010), RA according to the 2010 classification criteria for RA; SD, standard deviation; VAS, visual analogue scale.

(p<0.001). Large joint (all other joints) involvement was found in similar percentages of RA and UA patients (73% versus 68%, p=0.22). Patients with large joint involvement had more affected small joints (median (IQR) 10 (6-17) versus 7 (4-11), p<0.001) and achieved less often remission than patients without large joint involvement (57% versus 76%, p<0.001).

Predictors for remission

Significant univariate clinical predictors for achieving remission in the total study population were baseline DAS, HAQ, symptom duration, male sex, ACPA positivity, number of affected

Table 4a: Univariate logistic regression analyses with remission after 4 months (yes/no) as dependent variable.

Univariate regression	Odds ratio	95% CI
Classified RA (2010)	0.85	0.56 - 1.30
Baseline DAS	0.49	0.40 - 0.60
Baseline HAQ	0.43	0.33 - 0.57
Small joints*	0.93	0.90 - 0.95
Large joints**	0.72	0.65 - 0.79
Symptom duration (weeks)	0.99	0.99 - 1.00
ACPA positivity	1.59	1.14 - 2.23
Age (years)	1.00	0.99 - 1.02
Male sex	2.19	1.50 - 3.20
BMI (kg/m^2)	0.94	0.90 - 0.98

*number of swollen and/or tender small joints (metacarpophalangeal joints, proximal interphalangeal joints, thumb interphalangeal joints, wrists, second through fifth metacarpophalangeal joints)
** number of swollen and/or tender large joints (shoulders, elbows, hips, knees, ankles)
BMI, body mass index; CI, confidence interval; DAS, disease activity score; HAQ, health assessment questionnaire; RA (2010), RA according to the 2010 ACR/EULAR classification criteria.

Table 4b: Multivariate logistic regression analyses with remission after 4 months (yes/no) as dependent variable.

Multivariate regression	Analysis with DAS		Analysis with small and large joints	
	Odds ratio	95% CI	Odds ratio	95% CI
Baseline DAS	0.61	0.47-0.78	-	-
Small joints*	-	-	0.96	0.93-0.99
Large joints**	-	-	0.81	0.72-0.90
Baseline HAQ	0.66	0.46-0.94	0.63	0.46-0.88
Symptom duration (weeks)	0.99	0.98-0.997	0.99	0.98-0.997
ACPA positivity	1.59	1.09-2.33	1.44	0.98-2.12
Male sex	2.03	1.34-3.08	2.01	1.32-3.07
BMI (kg/m^2)	0.94	0.90-0.98	0.94	0.90-0.98

*number of swollen and/or tender small joints (metacarpophalangeal joints, proximal interphalangeal joints, thumb interphalangeal joints, wrists, second through fifth metacarpophalangeal joints)
** number of swollen and/or tender large joints (shoulders, elbows, hips, knees, ankles)
ACPA, anti-citrullinated protein antibodies; BMI, body mass index; CI, confidence interval; DAS, disease activity score; HAQ, health assessment questionnaire.

small joints, number of affected large joints and body mass index (BMI).(table 4) Fulfilling the 1987 or 2010 classification criteria for RA was not a predictor of remission. In a multivariate regression analysis including baseline DAS and excluding number of affected small and large joints, independent predictors were baseline DAS, HAQ, symptom duration, ACPA positivity, male sex and BMI. In a model including the baseline numbers of affected small and large

joints instead of the DAS, the number of affected small and large joints were both predictive, independently of each other. In this analysis, ACPA positivity was not an independent predictor.(table 4)

ACR/EULAR preliminary definition of remission

According to the preliminary ACR/EULAR definition [20] 157/610 (26%) of the patients achieved remission after four months (34 patients could not be defined because of missing data), without a difference between UA and RA patients (29/122 (24%) versus 126/479 (26%), p=0.45).

Mean (SD) DAS after four months of patients in ACR/EULAR remission is 0.82 (0.41).

206/610 (34%) patients did achieve DAS remission but were not in ACR/EULAR remission. They had a median (IQR) TJC of 0 (0-1), a median (IQR) SJC of 0 (0-0), a median (IQR) CRP of 5 (3-9) and a mean (SD) VAS general health of 21(14).

Table 5: Numbers of adverse events reported during 4 months of treatment with MTX and a tapered high dose of prednisone.

Numbers of adverse events	
Gastro-intestinal symptoms	98
Nausea	47/98
Liver enzyme elevations	45
Infectious	80
Upper airway tract	26/80
Gastro-intestinal	18/80
Skin/mucosa infection	8/80
Pneumonia	9/80
Urinary tract infection	7/80
Influenza/fever	7/80
Skin/mucosa	75
Hair loss	19/75
Rash	16/75
Stomatitis	9/75
Central Nervous System	73
Headache	18/73
Dizziness	11/73
Mood disorders	21/73
Cardiovascular	45
Hypertension	20/45
Metabolic	21
Pulmonary	21
Urogenital	8
Hematologic	5

152/610 (25%) patients achieved remission by both criteria, 201/610 (33%) did not achieve remission according to either and 5/610 (0.8%) patients were in ACR/EULAR remission but not DAS remission, based on arthritis in the feet (not included in the ACR/EULAR remission definition).

The data suggest that the ACR/EULAR definition of remission is more stringent than DAS-remission, resulting in lower remission percentages. Clinical and radiological follow-up is needed to show which definition is most adequate.

Adverse events

During 4 months of treatment 341/610 (56%) of the patients reported one or more adverse events (table 5). There were 16 serious adverse events in 16 (3%) of 610 patients (8 per 100 patient years). Two patients died: a 70 year old female from a myocardial infarction later found to be caused by giant cell arteriitis (incorrect inclusion due to alternative diagnosis), and an 85 year old female after refusing treatment for pneumonia. Fourteen hospital admissions were reported for patients with bacterial coxarthritis, Pneumocystis Carinii Pneumonia (a patient with pre-existing Non-Specific Interstitial Pneumonia), other pneumonia (3 patients), viral pneumonitis, urothelial cell carcinoma, surgery for carcinoma of the cecum, diverticulitis, bleeding from a benign intestinal polyp, supraventricular tachycardia, hypertension, peripheral arterial occlusion and pulmonary embolism.

DISCUSSION

Initial treatment with MTX and a tapered high dose of prednisone results in similar remission rates in 2010 classified and 1987 classified RA patients and in UA patients after four months. The majority (90%) of the patients showed no radiological progression after four months. Independent predictors for remission were low baseline DAS, low numbers of affected large and small joints, ACPA positivity, male sex and BMI.

The early remission rate of 61% is higher than previously reported in cohorts such as Combinatietherapie Bij Reumatoide Artritis (COBRA) and Behandel Strategieën (BeSt), where patients also received MTX and a tapered high dose of prednisone, combined with sulfasalazine.[3,11] This is most likely explained by our intentional inclusion of patients with milder disease activity and not (yet) fulfilling the classification criteria for RA. Also, our patients had on average a shorter symptom duration. Thus, the higher remission rate in this study would support the window of opportunity theory. However, earlier inclusion may have over classified patients who possibly had self-limiting disease.[8] Other possible explanations are the initial dose of methotrexate (25 mg/week compared to 7.5 mg/week in the other cohorts) and the absence of sulfasalazine in the initial drug combination.

The 2010 ACR/EULAR classification criteria were formulated to classify patients earlier in disease course.[7] In this study however, the symptom duration of patients classified as RA according to the 1987 or the 2010 criteria is comparable, which might explain why we found no difference in clinical response and remission rates between the groups, even though the 2010 criteria classified 19% more patients.

Also, we found no difference in remission rates between RA and UA patients, although we hypothesized that UA patients, as presumably very early RA, would benefit more from early combination therapy, and despite the facts that UA patients had a lower mean baseline disease activity and were predominantly male. This may be explained by the comparable symptom duration in UA and RA patients. Of the UA patients 64% had a symptom duration >12 weeks, thus possibly missing the so called window of opportunity.[21] Also, only a few UA patients were ACPA positive, compared to 68% in the RA group, and ACPA positivity in the total study population was found to be a predictor of achieving remission. ACPA negative RA and ACPA negative UA both may represent or include illnesses that do not sufficiently respond to combination therapy with MTX and prednisone and require different treatments.[22] Previously, in the PRObable rheumatoid arthritis: Methotrexate versus Placebo Treatment (PROMPT) study ACPA negative UA patients did not benefit from treatment with methotrexate monotherapy.[10]

The baseline characteristics in this study population suggest that classifying patients as RA by the new classification criteria rests predominantly on numbers of (small) joints involved and ACPA positivity, with UA patients having less joints involved and almost all UA patients being ACPA negative. ACPA negative patients who were still classified as RA had a higher disease activity and a longer symptom duration than ACPA positive RA patients. These characteristics may explain why ACPA negative RA patients achieve less remission than ACPA positive RA patients. It is possible that they might have benefited more from treatment if they were treated earlier.

As shown in previous studies, male patients achieve more remission than female patients.[23] Our results show that male sex is an independent predictor of remission and not associated with a lower pain score or tender joint count. Also a lower body mass index (BMI) was found to be an independent predictor of remission, which may be related to relative under dosing of patients with a high BMI.

The early and intensive treatment with a high dose of methotrexate and a tapered high dose of prednisone in this study was accompanied by adverse events in more than half (56%) of the patients. Although most adverse events were mild, serious adverse events were reported in 3% of patients. Two elderly patients died, one from pneumonia that may have been treatment related and on the patient's request remained untreated, one of a vasculitis related cardiac event. This patient thus was misdiagnosed, and, since the lethal event occurred during treatment with the tapered dose of prednisone, possibly under dosed.

In conclusion, initial therapy with MTX and a tapered high dose of prednisone results in high remission percentages (about 60%) both in early RA patients (regardless of classification according to the 1987 or 2010 criteria) and in UA patients after four months of treatment. Independent predictors for remission, besides male sex and low BMI, indicate that initiation of treatment while disease activity is relatively low results in more remission, regardless of whether patients fulfil the classification criteria for RA. ACPA negative patients may benefit from early treatment, but on the whole achieve less remission on MTX with prednisone than ACPA positive patients. This may indicate that this subgroup of patients represents a different disease, for which the optimal treatment remains to be determined.

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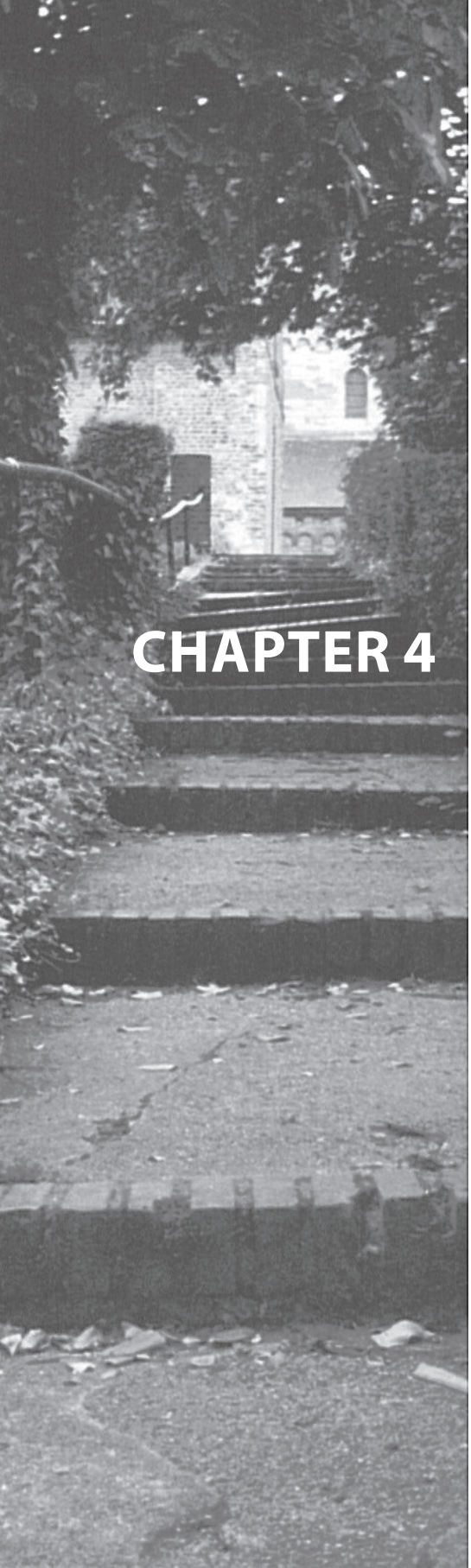

CHAPTER 4

A two-step treatment strategy trial in early arthritis patients aimed at achieving remission - the IMPROVED study

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ABSTRACT

Objective

To assess which treatment strategy is most effective in inducing remission in early (rheumatoid) arthritis.

Methods

Six-hundred-ten patients with early rheumatoid arthritis (RA-2010 criteria) or undifferentiated arthritis (UA) started with methotrexate (MTX) and a tapered high dose of prednisone. Patients in early remission (Disease Activity Score (DAS) <1.6 after 4 months) tapered prednisone to zero and with persistent remission after 8 months, tapered and stopped MTX. Patients not in early remission were randomized to either MTX plus hydroxychloroquine plus sulphasalazine plus low dose prednisone (arm 1) or to MTX plus adalimumab (arm 2). In case of remission after 8 months both arms tapered to MTX monotherapy, if not, arm 1 changed to MTX plus adalimumab and arm 2 increased adalimumab. Remission rates were compared between arms and between RA and UA patients, as were functional and radiological outcomes.

Results

Of all patients, 61% achieved early remission. After 1 year 68% of those were in remission and 32% in drug free remission. Of the randomized patients, 25% in arm 1 and 41% in arm 2 achieved remission at year 1 ($p<0.01$). Outcomes were comparable between RA and UA patients.

Conclusions

Initial MTX and prednisone resulted in early remission in 61% of patients with early (rheumatoid) arthritis. Of those, 68% are in remission and 32% were in drug free remission after 1 year. In patients not in early remission, earlier introduction of adalimumab resulted in more remission at year 1 than first treating with DMARD combination therapy plus prednisone.

INTRODUCTION

The way patients with rheumatoid arthritis (RA) are treated has changed dramatically over the last decades. Early and tight controlled treatment with disease modifying anti-rheumatic drugs (DMARDs), targeted to low disease activity, suppresses inflammation better than ever before, resulting in improved functional ability and minimized radiological joint damage.[1-6] Even remission can be achieved. Early combination therapy with synthetic DMARD treatment plus prednisone or a tumor necrosis factor alpha (TNF-α) inhibitor is most effective in most patients.[7-9]

It is thought that there is a 'window of opportunity' during which initiation of effective treatment may prevent inflammatory symptoms to become chronic and damaging to bone and joint tissues. To enable earlier diagnosis and treatment initiation, classification criteria for RA were revised in 2010.[10] Starting anti-rheumatic treatment already in the stage of undifferentiated arthritis (UA), when RA is still unclassifiable, might be useful.[7]

Treatment of UA patients with methotrexate (MTX) was successful in postponing but not preventing progression to RA.[12] It is possible that, as in RA patients, initial combination therapy with MTX and prednisone is more effective.[8,13] If patients do not achieve remission on initial combination therapy, the best follow up strategy needs to be determined: either expansion of DMARDs or switching to MTX with a TNF-α inhibitor, both proven effective in established RA.[6,9]

We designed a two-step treatment strategy study (remission induction therapy followed by randomization for patients who did not achieve remission) in patients with recent onset RA or UA, to determine how often remission or even drug free remission (DFR) can be achieved. Here we report clinical and radiological outcomes after 1 year.

METHODS

Study design and patients

The IMPROVED-study (acronym for Induction therapy with Methotrexate and Prednisone in Rheumatoid Or Very Early arthritic Disease, ISRCTN Register number 11916566 and EudraCT number 2006-006186-16) is a multicentre, randomized, single-blinded clinical trial designed by Dutch rheumatologists participating in the Foundation for Applied Rheumatology Research (FARR). Patients were recruited between March 2007 and September 2010 in 12 hospitals in the Western part of the Netherlands. Medical Ethics Committees of each participating centre approved the study protocol and all patients gave written informed consent.

Patients with both UA and early RA were included. Detailed in- and exclusion criteria were previously published.[8] Recent onset RA was defined according to the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 2010 classification

criteria [10] with symptom duration ≤2 years. UA patients had at least 1 joint clinically assessed as 'arthritis' and at least 1 other tender joint, in the opinion of the rheumatologist clinically suspected to represent early RA but not fulfilling the 2010 ACR/EULAR criteria.

Intervention

The treatment target was clinical remission, defined as a DAS <1.6.[11] Four-monthly DAS assessments were performed by trained nurses who were blinded for allocated treatment. Patients and doctors were not blinded for practical reasons. All patients started with four months of open-label MTX 25 mg/week (dose escalated from 7.5 mg/week in 4 weeks) and prednisone tapered in 7 weeks from 60 mg/day to a stable dose of 7.5 mg/day. Patients in 'early DAS-remission' (defined as DAS <1.6 at 4 months) tapered prednisone to zero in 3 weeks and when still in remission at 8 months, also tapered MTX to zero in 9 weeks. In case of a DAS ≥1.6 after stopping prednisone, it was restarted at 7.5 mg/day.(figure 1)

Patients not in early remission at 4 months were randomized either to MTX 25 mg/week plus hydroxychloroquine (HCQ) 400 mg/day, sulphasalazine (SSZ) 2000 mg/day and prednisone 7.5 mg/day (arm 1) or to MTX 25 mg/week plus adalimumab 40 mg/2weeks (arm 2). If in remission at 8 months, patients in arm 1 started tapering prednisone and subsequently SSZ and HCQ to MTX monotherapy, patients in arm 2 tapered adalimumab to MTX monotherapy. If not in remission at 8 months, patients in arm 1 switched to MTX+adalimumab (40 mg/2weeks), patients in arm 2 increased adalimumab to 40 mg/week.(figure 1)

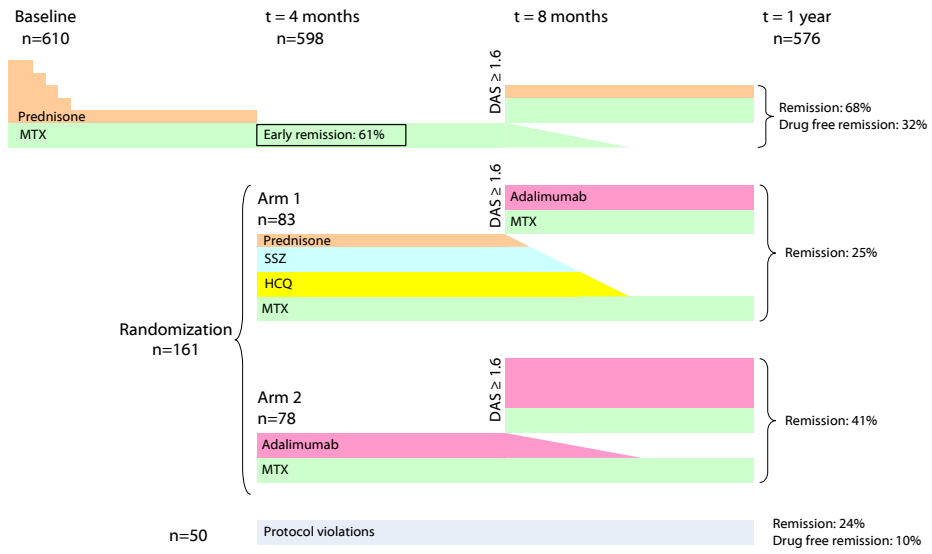

Figure 1. Study flow chart with percentages DAS-remission after the first study year.
DAS, disease activity score; HCQ, hydroxychloroquine; MTX, methotrexate; Remission, DAS ≤1.6; SSZ, sulfasalazine.

Patients who did not regain remission after restarting prednisone, were also randomized ('delayed randomization') as described above.

Variable block randomization stratified per centre and diagnosis ensured numerical equality of the two randomization arms. Randomization sequence was obtained by computer. At the local centres, allocation was performed by the rheumatologists drawing opaque envelops.

Study outcomes and assessments

Primary outcomes after 1 year were percentages of clinical and DFR based on a DAS <1.6.[11] A provisional Boolean based remission definition published by the ACR/EULAR [12] based on the 44 joint count was used to recalculate remission percentages at 4, 8 and 12 months. Secondary outcomes collected 4 monthly were DAS, functional ability measured with the Health Assessment Questionnaire (HAQ, ranging from 0 (best) to 3 (worst), ≥0.2 points change is clinically relevant)[13], radiological damage progression measured with Sharp-van der Heijde score (SHS, ranging from 0-448, progression was defined as an increase in SHS ≥0.5 point)[14] and toxicity. Radiographs of hands and feet, blinded for patient identity, were scored for the presence of erosions and joint space narrowing in time random order by 2 trained, independent readers (KW and LH). Since 88% of patients showed no progression, intra-class correlation coefficients were not suitable for measuring reliability.[15] In 83% of patients both readers scored the same progression. In 54 patients with inter-reader differences ≥2 (the median difference in progression score of patients in which both readers scored different progression) a consensus score was reached.

Outcomes were reported separately for patients who achieved early DAS-remission and those randomized, and were compared between randomization arms. Additional comparisons were made between RA and UA patients. Patients who were not in early DAS-remission and who were not randomized according to the protocol were analysed in the Outside of Protocol group. Reasons for protocol deviation were not inventoried.

Statistical analysis

With a power calculation we assessed the number of patients needed in each randomization arm to detect differences between arms of at least 50% in remission rates and 0.2 points in HAQ with a power of 80%. Based on previous studies [9,16,17] we estimated 30% of the patients would achieve early remission. We needed 535 patients to randomize at least 100 patients per arm. Because during the study early DAS-remission rates were higher, the inclusion number was extended to 610 patients.

We performed intention-to-treat analyses. Outcomes were analysed using students T tests, Mann Whitney U tests and chi square tests. DAS and HAQ over time were compared using linear mixed models, with treatment strategy (arm 1 and 2) and time (study visit) as fixed effects, in an unstructured covariance structure. Statistical analyses were conducted with SPSS for Windows version 20.0.

RESULTS

Study profile

In total 610 patients were included, 479 (79%) with RA and 122 (20%) with UA and 9 patients could not be classified because of missing values. Over the year 23 patients withdrew consent, 3 discontinued because of a revised diagnosis and 6 because of co-morbidity. Twelve of these patients dropped out during the first 4 months.

After 4 months, 375/610 patients (61%) had a DAS <1.6 (early DAS-remission). Twelve other patients with a marginally high DAS at 4 months were by protocol reassessed after 1 month. All then had a DAS <1.6 and were included in the early remission group, bringing it to a total of 387 patients, 291/479 (61%) RA patients and 79/122 (65%) UA patients were in early remission (12 patients were lost to follow up and 5 were not classifiable because of missing data). One-hundred-forty-four/387 (37%) (114/291 (39%) with RA and 28/79 (35%) with UA, 2 had missing data) also fulfilled the proposed ACR/EULAR remission definition.

In total, 161/610 (26%) patients not in DAS-remission were randomized, 83 patients into arm 1 and 78 to arm 2. None fulfilled the proposed ACR/EULAR remission definition. Two patients with a missing DAS at 4 months and 48 other patients with a DAS ≥1.6 at 4 months who did not follow the protocol were analysed in the Outside of Protocol (OP) group. Thirty-three of these patients tapered prednisone and in 17 patients various other treatment decisions were made.

Clinical characteristics at baseline and 4 months

Patients who achieved early DAS-remission had lower mean baseline DAS, HAQ and DAS-components, were more often male and anti-citrullinated protein antibodies (ACPA) positive and had a shorter symptom duration than randomized patients.[8] Clinical characteristics at baseline and 4 months were comparable in arm 1 and 2.(table 1)

Outcomes after 1 year

After 1 year, 328/610 (54%) patients achieved DAS-remission (253/479 (53%) RA patients versus 71/122 (58%) UA patients (p=0.10), 4 patients were not classifiable. Proposed ACR/EULAR remission was achieved in 144/610 (24%). Drug free remission (DFR) after 1 year was achieved in 130/610 (21%) patients (93/479 (19%) RA patients, 36/122 (30%) UA patients, 1 patient was not classifiable). In the early DAS-remission group patients most often achieved DAS-remission. Patients in arm 1 less often achieved DAS-remission than patients in arm 2 (p=0.01) (table 1).

After 1 year, mean HAQ and DAS were lower in the early DAS-remission group than in arm 1 and 2. Over time, no significant difference in DAS and HAQ between arms 1 and 2 was present (mean DAS difference of 0.03 (95%CI -0.16;0.22), mean HAQ difference 0.04 (95%CI 0.01;0.29)).

Table 1. Baseline characteristics and clinical outcomes per treatment group.

	Early DAS-remission	Randomization		Outside protocol treatment
		Arm 1	Arm 2	
Baseline characteristics	n = 387	n = 83	n = 78	n = 50
DAS, mean ± SD	3.0 ± 0.8	3.6 ± 0.9	3.6 ±1.0	3.6 ±0.9
HAQ, mean ± SD	1.0±0.7	1.4±0.6	1.4±0.6	1.3 ±0.7
Swollen Joint Count, median (IQR)	5 (2-9)	6 (3-10)	8 (4-12)	7 (3-13)
Tender Jont Count, median (IQR)	5 (3-8)	8 (6-13)	9 (6-13)	8 (6-14)
Age in years, mean ± SD	52±14	49±14	51±14	54±14
Female, no (%)	240 (62)	64 (77)	58 (74)	42 (84)
Symptom duration in weeks, median (IQR)	17 (9-30)	22 (9-41)	21 (8-31)	18 (9-42)
Symptom duration <12 weeks, no (%)	247 (64)	59 (71)	49 (63)	28 (56)
RF positive, no (%)	224 (58)	41 (49)	43 (55)	23 (46)
ACPA positive, no (%)	225 (58)	40 (48)	37 (47)	25 (50)
RA(2010), no (%)	298 (77)	66 (80)	66 (85)	40 (80)
Total SHS, median (IQR)	0 (0-0.5)	0 (0-0)	0 (0-0)	0 (0-0)
Erosive, no (%)	63 (16)	10 (12)	13 (17)	3 (6)
4 months follow up				
DAS, mean ± SD	1.0±0.4	2.5±0.6	2.6±0.7	2.3±0.6
HAQ, mean ± SD	0.2±0.3	0.9± 0.6	0.9±0.6	0.8±0.7
Swollen Joint Count, median (IQR)	0 (0-0)	1 (0-4)	2 (1-5)	0 (0-2)
Tender Joint Count, median (IQR)	0 (0-1)	4 (3-7)	5 (3-9)	4 (2-6)
ESR mm/hr, median (IQR)	6 (3-12)	13 (7-22)	11 (6-19)	15 (9-28)
VAS global health in mm, mean ± SD	14±14	37±21	38±21	30±21
1 year follow up				
DAS, mean ± SD	1.3±0.8	2.1±0.9	1.8±0.9	2.1±0.8
HAQ, mean ± SD	0.4 ±0.5	0.9±0.6	0.8±0.7	0.8±0.6
Swollen Joint Count, median (IQR)	0 (0-1)	0 (0-3)	0 (0-1)	1 (0-2)
Tender Joint Count, median (IQR)	0 (0-2)	3 (1-7)	3 (0-6)	4 (1-8)
ESR mm/hr, median (IQR)	8 (4-15)	9 (5-18)	9 (4-16)	14 (7-31)
VAS global health in mm, mean ± SD	20±21	33±23	27±20	33±24
Total SHS, median (IQR)	0 (0-0.5)	0 (0-0.5)	0 (0-0)	0 (0-0)
Erosive, no (%)	65 (17)	12 (15)	12 (16)	2 (4)
DAS-Remission, no (%)	263 (68)	21 (25)	32 (41)*	12 (24)
Drug free remission, no (%)	124 (32)	1 (1)	0 (0)	5 (10)
ACR/EULAR remission, no (%)	122 (32)	9 (11)	13 (17)	4 (8)
SHS progression, median (IQR)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)

*p-value <0.05 between arm 1 and arm 2. After 4 months 12 patients were lost to follow up and 598 patients were categorized a described in this table.

ACPA, anti-citrullinated protein antibodies; DAS, disease activity score; DAS-remission, DAS <1.6; ACR/EULAR remission, provisional Boolean based remission definition published by the American College of Rheumatology and the European League Against Rheumatism based on a 44 joint count; Erosive denotes the presence of at least 1 erosion on radiographs of hands and feet; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; IQR; interquartile ranges; no, number; Progression, increase in SHS ≥0.5 points; RF, rheumatoid factor; RA(2010), rheumatoid arthritis according to the 2010 classification criteria; SD, standard deviation; SHS, Sharp- van de Heijde Score; VAS, visual analogue scale.

Median (IQR) SHS progression score in all groups was 0 (0-0) without a difference between UA and RA patients. Of the total study population, 33/610 (5%) had radiological progression defined as an increase in SHS ≥0.5 point, 20/387 (5%) in the early remission group, 5/83 (6%) in arm 1, 6/78 (8%) in arm 2 and 2/50 (4%) in the OP group. Only 1 patient, categorized in the early DAS-remission group and losing remission at 8 months, had rapid radiological progression (defined as a progression score of ≥5 points in 1 year) of 18 points.

Loss of early DAS-remission after prednisone discontinuation

Fifteen of 387 patients who achieved early DAS-remission did not taper and stop prednisone. Of the other 372 patients, 109 (29%) lost DAS-remission at 8 months of which 67 restarted prednisone at 7.5 mg/day. In 40 patients the protocol was not followed and various other steps were taken. Two patients had missing data. After 1 year, 48/67 (72%) of the patients re-treated according to protocol and 22/40 (55%) of those treated otherwise had again achieved remission.

Results at 8 months

DAS-remission at 8 months was achieved in 30/83 (36%) in arm 1 and 27/78 (35%) in arm 2 (p=0.99). In arm 1, 30 patients tapered to monotherapy, 33 switched to adalimumab and in 19 patients other steps were taken (1 patient had missing data). In arm 2, 26 patients tapered to monotherapy, 28 increased adalimumab and in 21 patients other steps were taken (3 patients had missing data). More patients in arm 2 who increased adalimumab achieved DAS-remission after 1 year, than patients in arm 1 who switched to adalimumab (8/28 (29%) versus 6/33 (18%) (p=0.29)). In addition, more patients in arm 2 retained DAS-remission after tapering to MTX monotherapy than in arm 1 (17/26 (65%) versus 11/30 (37%) respectively, p=0.02).

Subgroups

During the first year of the study 96/610 (16%) patients never achieved DAS-remission, 462/610 (76%) achieved DAS-remission at least once and 52 patients had one or more missing DAS-values during the first year. Compared to those who achieved DAS-remission at least once, patients who never achieved DAS-remission had a higher mean baseline DAS (mean (SD) 3.7 (0.9) versus 3.1 (0.9), p<0.001), a longer median symptom duration (median (IQR) 24 (12-44) versus 17 (8-31) weeks, p=0.002) and included more females (85/96 (89%) versus 291/462 (63%), p<0.001) and fewer ACPA-positives (45/96 (47%) versus 265/462 (57%), p=0.047).

Adverse events

During the first 4 months there were 471 adverse events (AE) in 341/610 (56%) patients, including 2 deaths and 14 other serious adverse events (SAE) in 14 patients.[8]

Table 2. Number of adverse events reported between 4 months and 1 year for patients in the early DAS-remission group, the randomization arms and the outside protocol group.

	Early remission n=387	**Arm 1 n=83**	**Arm 2 n=78**	**Outside protocol n=50**
Patients with AE*, no (%)	205/387 (53%)	61/83 (74%)	52/78 (68%)	28/50 (56%)
Total number of AE	298	101	88	40
Type of AE				
Cardiovascular	9	5	6	1
Pulmonary	11	-	2	1
Gastrointestinal	62	18	20	8
Nausea/emesis	15	6	5	2
Increased liver enzymes	33	5	9	3
Other	14	7	6	3
Neuropsychiatric	22	17	2	4
Headache	2	7	-	-
Dizziness	10	1	-	2
Mood disorders	6	5	1	-
Other	4	4	1	2
Urogenital	5	2	2	1
Skin/mucous membranes	51	6	13	3
Rash	20	5	6	2
Hair thinning/loss	8	1	2	1
Sicca complaints	5	-	1	-
Stomatitis	4	-	-	-
Other	14	-	4	-
Infections	76	23	27	11
Upper airway tract	17	4	8	5
Gastro-intestinal	4	-	3	-
Skin/mucosa	11	2	1	1
Pneumonia / bronchitis	8	3	1	1
Urinary tract	9	6	5	1
Flu/unspecified fever	10	2	2	2
Other	17	6	7	1
Trauma/injury	15	3	-	2
Surgical procedures without hospitalization	9	3	2	2
Other	38	24	14	7

*One or more adverse events possible per patient.

AE: adverse event; no, number.

From 4 months to 1 year, 346/610 (57%) patients reported 527 AE, 53% in the early DAS-remission patients, 74% in arm 1, 68% in arm 2 (arm 1 versus arm 2 p=0.41) and 56% in the OP-group. The most common AE in all groups were increased liver enzymes, nausea, upper airway and skin/mucosa infections and skin rashes (table 2). In 26/610 (4%) patients, serious adverse events were reported. Three patients died: one of a squamous cell carcinoma of the tongue (early remission group), one of a cerebral tumor (arm 2, treated with adalimumab 40 mg/2weeks for 4 months), and one patient of an ovarian carcinoma (OP-group; in the 7 months prior to diagnosis the patient was treated with MTX and with prednisone for 4 months). Three other malignancies were reported, all in the early remission group (breast carcinoma, basal cell carcinoma of the skin, malignant mesothelioma). Twenty-five hospital admissions were reported in 23/610 (3%) patients, 10 in the early remission group, 7 in arm 1, 6 in arm 2 and 2 in the OP group. Reasons for hospitalization were: complications of malignancy (3 patients, described above), pneumonia (4 patients; 2 in arm 1, 1 in arm 2 and 1 in the OP-group), suspicion of septic arthritis (arm 1, cultures remained negative), cellulitis of the lower leg (2 patients; early remission group and arm 1), percutaneous coronary intervention for cardiac ischemia (2 patients; early remission group and arm 2), cardiac arrhythmia (2 patients in the early remission group), urosepsis (arm 1), myocardial infarction (early remission group), femoral fracture (early remission group), total hip replacement for osteoarthritis (arm 1), lower leg amputation for peripheral vascular disease due to diabetes mellitus (OP-group), exacerbation of chronic obstructive pulmonary disease (arm 2), surgery for cervical spinal disc herniation (early remission group), cerebrovascular accident (arm 2), Nissen fundoplication (arm 2), femural head necrosis (arm 2) and trauma due to a car accident (arm 1).

DISCUSSION

In patients with early arthritis, remission defined by DAS can be achieved in 54% after 1 year with initial treatment with MTX and a tapered high dose of prednisone followed by remission steered treatment adjustments. Radiological damage progression was effectively suppressed in almost all patients. Of the 61% of patients who started tapering medication after being in remission after 4 months, 68% were in remission and 32% in drug free remission (DFR) after 1 year. These results suggest that combination therapy with MTX and a tapered high dose of prednisone can halt the potentially chronic disease course of rheumatoid arthritis, prevent damage and induce DFR.

Remission is more difficult to achieve if the initial treatment was unsuccessful. For those patients who did not achieve early remission, an early switch to a combination of MTX with adalimumab resulted in more remission (41% versus 25%) than treatment expansion with SSZ and HCQ, reserving adalimumab as possible next step. Functional ability, radiological damage progression and toxicity were similar.

This study is the first to steer at remission in patients with early RA and taper and stop medication as soon and as long as this is achieved. The overall remission rate of 54% after 1 year is high. Few other studies reported similar percentages, and there treatment was continued longer and none tapered medication or achieved early DFR.[17-20]

A possible explanation for the high (drug free) remission rates and the minimal radiological damage progression is that we included patients in a relatively early and possibly reversible disease stage which may represent the 'window of opportunity'.[21] Maybe in this stage, chronicity and damage can be prevented or reversed. It is also possible that some patients with UA or even classified as RA might have had a self-limiting type of arthritis.[22] A second explanation may be that we included patients with relatively low disease activity, who will more easily achieve the target of a DAS <1.6.[8,23] The final explanation might be the treatment chosen, initially with a rapidly built up high dose of MTX and a high dose of prednisone tapered to 7.5 mg/day - a combination proven superior to DMARD monotherapy in patients with RA [6,24,25] - followed after randomization by progressive therapies either with multiple DMARDs or with a TNF-inhibitor, proven to be effective both in early and established RA.[26-28]

We used the DAS criteria to define remission, which are less stringent than the provisional remission criteria proposed by the American and European Rheumatology associations. Nonetheless, we have shown that our patients in DAS-remission have good functional ability and virtually no damage progression.

After 1 year significantly more patients in arm 2 had achieved DAS-remission than in arm 1, although after 8 months the remission rates were similar. The 1 year difference is explained by more patients losing remission after tapering low dose prednisone and poly-DMARDs to MTX monotherapy and less patients achieving remission after switching from poly-DMARDs and prednisone to adalimumab (both in arm 1). This suggests that if remission is not achieved on initial combination therapy, it is better to introduce adalimumab early. It appears that patients who fail on prednisone and poly-DMARDs may respond less well to any other treatment, as was previously demonstrated in a comparison of initial or delayed treatment with infliximab in patients with recent onset RA (1987 classification criteria).[29]

Although prednisone in the initial treatment combination appears to be very effective, it may also have several side effects and therefore our results may come at a price. Fourteen serious adverse events (infections, cardiovascular disease, femoral head necrosis, diabetic complications) might be related to the use of prednisone. Thirty-six % of our patients did not achieve DAS-remission on the initial treatment, and 16% did not achieve DAS-remission on any treatment step. Other (biologic) therapies may be more effective and less toxic.

In this trial, which integrated treatment adjustments by protocol with daily practice, the treating rheumatologist sometimes disagreed with required treatment steps based on DAS evaluations by nurses who were blind for treatment. In some cases the patients refused to take the next treatment step. Despite the protocol deviations that ensued, in general, treat-

ment remained steered at DAS-remission or clinical remission, and follow up visits continued as before. Because we included all data in our analyses, no information was lost.

In conclusion, the majority of patients with early rheumatoid arthritis can achieve remission with initial combination therapy followed by treatment targeted at remission early in the disease course. Of the 61% of patients who achieve remission on initial treatment and start tapering medication, 68% are in remission and 32% are in drug free remission after 1 year. For patients not in early remission, combination therapy including adalimumab resulted in significantly more remission after 1 year than combination therapy with poly-DMARDs. Overall, in all patients functional ability was preserved and radiographic damage progression was minimal. This study suggests that, if diagnosed and treated early, rheumatoid arthritis may not progress to the chronic and destructive autoimmune disease as we knew it.

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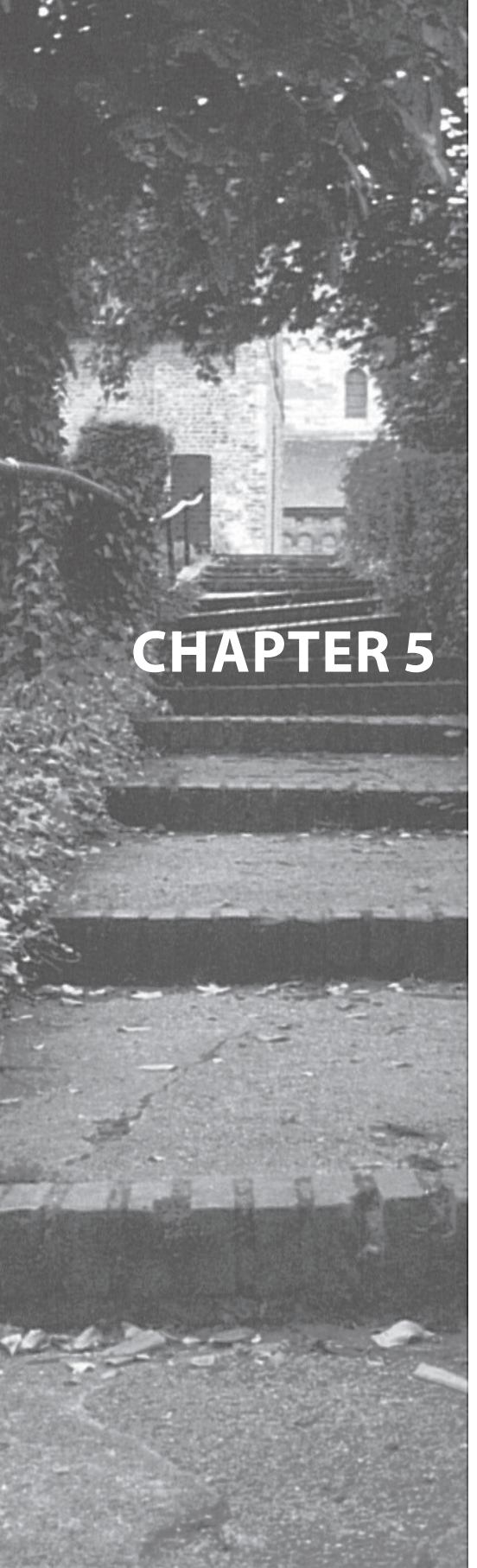

CHAPTER 5

Health related quality of life and functional ability in patients with early arthritis during remission steered treatment – results of the IMPROVED study

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ABSTRACT

Introduction

To investigate patient reported outcomes (PROs) of functional ability and health related quality of life (HRQoL) in patients with early (rheumatoid) arthritis during 1 year of remission steered treatment.

Methods

Six-hundred-ten patients with early rheumatoid (RA) or undifferentiated arthritis (UA) were treated with methotrexate (MTX) and tapered high dose of prednisone. Patients in early remission (Disease Activity Score (DAS) <1.6 after 4 months) tapered prednisone to zero and when in persistent remission, also tapered MTX. Patients not in early remission were randomized to either MTX+hydroxychloroquine+sulphasalazine+prednisone (arm 1) or to MTX+adalimumab (arm 2). Every 4 months, patients filled out the Health Assessment Questionnaire (HAQ) and the McMaster-Toronto Arthritis Patients Preference Questionnaire (MACTAR), the Short Form 36 (SF-36) and visual analogue scales (VAS). Change scores were compared between treatment groups. The association with achieving remission was analyzed using linear mixed models.

Results

During year 1, patients who achieved early remission had the most improvement in PROs with scores comparable to the general population. Patients in the randomization arms showed less improvement. Scores were comparable between the arms. There was a significant association between achieving remission and scores of HAQ, MACTAR and physical HRQoL.

Conclusions

In early arthritis, PROs of functional ability and HRQoL after 1 year remission steered treatment reach normal values in patients who achieved early remission. In patients not in early remission who were randomized to two strategy arms PROs improved less, with similar scores in both treatment arms.

INTRODUCTION

In rheumatoid arthritis (RA) treatment with disease modifying anti-rheumatic drugs (DMARDs) is targeted at achieving optimal suppression of disease activity. With that, clinical symptoms as well as radiological joint damage (progression) are prevented and patient reported outcomes (PROs) such as pain and health related quality of life (HRQoL), physical and mental wellbeing, improve.[1] Earlier studies have suggested that the better disease activity is suppressed, the better the outcomes of functioning and radiological joint damage progression.[2,3] Achieving clinical remission would ideally be associated with achieving PROs comparable to those in the general population.

In the IMPROVED study, anti-rheumatic treatment was targeted at remission. Patients with early (rheumatoid) arthritis were treated with initial combination therapy of methotrexate (MTX) and prednisone. If clinical remission (disease activity score (DAS) <1.6) was not achieved after 4 months, patients were randomized into two treatment arms: either starting with a combination of non-biologic DMARDs with low dose prednisone or with MTX and TNF-α inhibitor adalimumab. The aim of this sub-analysis was to measure change in functional ability and HRQoL during the first year of remission-steered treatment, to compare outcomes between the randomization arms and to compare study patients with the general population.

METHODS

Study design

The IMPROVED-study (acronym for Induction therapy with Methotrexate and Prednisone in Rheumatoid Or Very Early arthritic Disease) is a multicenter, randomized, single-blinded trial comparing two combination therapies in patients with recent onset arthritis aiming at clinical remission, defined as a DAS <1.6. The IMPROVED trial was designed and conducted by rheumatologists in the Foundation for Applied Rheumatology Research (FARR) and was registered in the ISRCTN Register (number 11916566) and the EudraCT (number 2006-006186-16).

Patients were recruited between March 2007 and September 2010 in 12 hospitals in the Western part of the Netherlands. The Medical Ethics Committee of each participating center approved the study protocol and all patients gave written informed consent. Patients with rheumatoid arthritis (RA) and patients with undifferentiated arthritis (UA) were included. RA was diagnosed according to the 2010 American College of Rheumatology (ACR) / European League Against Rheumatism (EULAR) classification criteria [4] with symptom duration of <2 years. UA was defined as 'arthritis' in at least one joint and one other painful joint in which no definitive diagnosis could be made, considered to have very early RA according to the

treating rheumatologist, regardless of symptom duration. All patients were ≥18 years old with a DAS ≥1.6. Detailed inclusion and exclusion criteria were previously described.[5]

All patients were initially treated for 4 months with MTX 25 mg/week and a tapered high dose of prednisone, starting with 60 mg/day, tapered to 7.5 mg/day in 7 weeks. Patients in early remission (DAS <1.6 after 4 months) tapered prednisone to 0 and when still in remission after 8 months, also tapered MTX to 0. Patients not in early remission (DAS ≥1.6) were randomized using variable block randomization stratified per centre to ensure numerical equality of the two treatment groups. Randomization sequence was obtained by computer. At the local centres, allocation was performed by drawing opaque envelopes from separate boxes for UA and RA. Patients were randomized to either a combination of either MTX 25 mg/week, hydroxychloroquine (HCQ) 400 mg/day, sulphasalazine (SSZ) 2000 mg/day and prednisone 7.5 mg/day (arm 1) or a combination of adalimumab 40 mg/2weeks and MTX 25 mg/week (arm 2). When patients did not achieve remission after 8 months, patients in arm 1 switched to MTX+ adalimumab and patients in arm 2 increased adalimumab to 40 mg/week. If patients achieved remission after 8 months, patients in both arms tapered to MTX monotherapy. Patients who did not achieve remission but were not randomized were analyzed in a separate group (outside of protocol (OP) group).[6]

Outcomes

Functional ability was assessed every 4 months with the Health Assessment Questionnaire (HAQ).[7] The HAQ score of a general (Finnish) population is 0.25.[8]

The McMaster-Toronto Arthritis Patients Preference Questionnaire (MACTAR) also measures functional ability. Patients have to rank five activities that are impaired because of their arthritis. Over time, improvement or deterioration of these five activities can be measured. The MACTAR is sensitive to change and useful to detect small differences. Compared to the baseline score, a higher score denotes improvement and a lower score means deterioration. The MACTAR interview from Canada was translated into Dutch in collaboration with the author of the original MACTAR. The translation was first used in the COBRA study, validated and judged as highly responsive.[9-11]

HRQoL was assessed using the Short-Form 36 (SF-36) focusing on 8 domains of health; physical functioning, role limitations due to physical or due to emotional functioning, bodily pain, general health, vitality, social functioning, mental health. The total score ranges from 0 (worst) to 100 (best). Two summary components scores, the mental component score (MCS) and the physical component scores (PCS), can be calculated from the 8 domains. These component scores are standardized, based on the worldwide population norm, to a mean of 50 and a standard deviation of 10.[12,13] The minimum clinically important difference to assess improvement or deterioration is a 5-10 point difference from baseline for the subscales and 2.5-5 points for the component scores.[14]

Various visual analogue scales (VAS) were used and patients had to indicate on a scale from 0 to 100 millimeters (0 means none, 100 means the worst) their appreciation of global health (VASgl), pain (VASpain), disease activity (VASda) and morning stiffness (VASms).

Statistical analyses

All outcomes were calculated according to the intention-to-treat (ITT) principle. All mean outcomes after 4 months, 8 months and 1 year were tested between arms 1 and 2 using the students *t*-test and to test the difference in remission rates we used the χ^2-test.

HAQ- and MACTAR scores, MCS, PCS and VAS measurements were reported separately for patients who achieved early remission and those randomized, and were compared between the randomization arms. The results of the study population were compared with those in the general population, if available.

Mean change scores over time were tested between the randomization arms using an independent Student's *t*-test. Clinically relevant improvement or deterioration after 1 year in HRQoL was assessed per treatment group, using the minimum clinically important difference.

To assess the relationship between achieving remission and the PROs SF36-PCS, SF36-MCS, HAQ and MACTAR a linear mixed model (with an unstructured covariance structure) was used. The analyses were first performed with an interaction term for remission achievement and treatment (early remission, arm 1, arm 2, OP group) because the different treatment strategies might influence remission achievement (as fixed effects were entered into the model: time (study visit at 4 months, 8 months and 1 year) and mean baseline score of the assessed PRO) In case of a significant interaction term, the analyses were stratified for treatment. The association between remission and PROs was assessed with and without adjustment for baseline variables anti-citrullinated protein antibodies (ACPA) status (positive/negative), sex (male/female), DAS at baseline, Tender Joint Count and Swollen Joint count. We used these determinants because they were identified as predictors for achieving remission after the first 4 months of the study.[5] As fixed effects were entered into the model: time (study visit at 4 months, 8 months and 1 year), mean baseline score of the assessed PRO and the determinants for which the analyses were adjusted. After the initial analysis defining remission as a DAS <1.6 we re-analysed the association with remission defined according to the provisional Boolean based remission definition published by the ACR/EULAR with a 44 joint count.[15]

Statistical analyses were conducted with SPSS for Windows version 20.0 (SPSS Inc., Chicago, Ill).

RESULTS

In total, 610 patients were included. During the first year, 32 patients left the trial (23 withdrew consent, 3 discontinued because of a revised diagnosis, 6 because of co-morbidity).

After 4 months, 387 (63%) achieved early remission (DAS <1.6). Of the 221 patients who did not achieve early remission, 161 patients were randomized; 83 patients into arm 1 (poly-DMARD), 78 to arm 2 (MTX+ adalimumab). Fifty patients did not achieve remission but were not randomized (outside of protocol (OP) group).[6] Patients who achieved early remission had a lower mean baseline DAS, lower values of all DAS-components, a shorter median symptom duration and included fewer females and more ACPA positive patients.[5](table 1)

After 1 year, remission was most often achieved by patients in the early remission group (68%). Fewer patients randomized to arm 1 achieved remission after 1 year than patients randomized to arm 2 (respectively 25% and 40%, p=0.01) (table 2).

Functional ability

HAQ scores in the early remission group were lower, indicating better functional ability, than in the randomization arms, both at baseline and after 1 year.(figure 1) Functional ability

Table 1. Baseline characteristics per treatment group.

	Early remission	Arm 1	Arm 2	OP group
Baseline	n = 387	n = 83	n = 78	n = 50
Age (years), mean ± SD	52 ± 14	48 ± 14	51 ± 14	54 ± 14
Female, n (%)	239 (62)	63 (76)	64 (82)	42 (84)
Symptom duration (weeks)	17 (9-30)	22 (9-40)	21 (8-29)	18 (9-42)
ACPA positive, n (%)	225 (58)	40 (48)	36 (46)	25 (50)
RA2010, n (%)	297 (77)	66 (80)	64 (82)	40 (80)
Erosive disease, n (%)	63 (16)	10 (12)	13 (17)	3 (6)
DAS, mean ± SD	3.0 ± 0.9	3.6 ± 0.9	3.6 ± 1.0	3.6 ± 0.9
Tender Joint Count, median (IQR)	5 (2-9)	6 (3-10)	8 (4-12)	7 (3-13)
Swollen Joint Count, median (IQR)	5 (3-8)	8 (6-13)	9 (6-13)	8 (6-14)
HAQ, mean ± SD	1.0 ± 0.7	1.4 ± 0.6	1.4 ± 0.65	1.3 ± 0.7
MCS, mean ± SD	51.2 ± 10.2	46.1 ± 12.4	48.8 ± 11.5	46.5± 13.3
PCS, mean ± SD	37.6 ± 9.3	33.0 ± 8.8	32.9 ± 8.9	35.2± 8.5
MACTAR, mean ± SD	50.1 ± 4.5	47.7 ± 4.6	48.1 ± 4.6	47.7 ± 5.2
VAS global (mm) , mean ± SD	43 ± 24	54 ± 20	54 ± 22	51 ± 22
VAS disease activity (mm) , mean ± SD	56 ± 25	66 ± 19	67 ± 22	66 ± 20
VAS pain (mm) , mean ± SD	50 ± 24	63 ± 19	61 ± 20	60 ± 24
VAS morning stiffness (mm) , mean ± SD	56 ± 27	69 ± 21	62 ± 25	54 ± 30

* p-value between arm 1 and 2. Data are presented as means and standard deviations (SD), medians and interquartile ranges (IQR), or numbers and percentages (%).
ACPA, anti-citrullinated protein antibody; DAS, disease activity score; HAQ, Health Assessment Questionnaire; MACTAR, McMaster-Toronto Arthritis Patients Preference Questionnaire; MCS, Mental Component Score; OP group, outside of protocol group; PSC, Physical Component Score; RA2010, rheumatoid arthritis according to the 2010 ACR/EULAR classification criteria; VAS, visual analogue scale.

Table 2. Patient reported outcomes during 1 year follow up per treatment group.

	Early remission	Arm 1	Arm 2	p*	OP group
	n=387	n=83	n=78		n=50
4 months follow up					
DAS	0.97 (0.40)	2.49 (0.63)	2.57 (0.68)	0.47	2.31 (0.63)
HAQ	0.23 (0.33)	0.86 (0.57)	0.88 (0.57)	0.77	0.73 (0.68)
MACTAR	58.2 (15.7)	52.8 (15.1)	48.9 (18.8)	0.14	51.6 (14.1)
MCS	52.4 (8.0)	48.8 (9.9)	50.7 (10.8)	0.26	49.8 (10.5)
PCS	51.7 (8.1)	39.4 (9.7)	38.1 (9.4)	0.44	42.5 (9.4)
VAS global (in mm)	14 (14)	37 (21)	39 (21)	0.61	28 (22)
VAS disease activity (in mm)	12 (15)	42 (24)	43 (24)	0.74	32 (25)
VAS pain (in mm)	10 (14)	39 (24)	38 (24)	0.79	27 (24)
VAS morning stiffness (in mm)	11 (17)	40 (27)	39 (27)	0.78	32 (30)
8 months follow up					
DAS	1.29 (0.69)	1.97 (0.87)	2.01 (0.91)	0.77	2.02 (0.84)
HAQ	0.35 (0.44)	0.74 (0.61)	0.81 (0.64)	0.51	0.68 (0.59)
MACTAR	56.4 (15.7)	55.8 (14.7)	54.5 (16.1)	0.60	48.9 (19.9)
MCS	52.9 (8.4)	46.6 (17.9)	48.7 (10.3)	0.85	48.5 (13.0)
PCS	48.9 (9.1)	42.8 (10.9)	42.5 (11.0)	0.26	43.7 (9.5)
VAS global (in mm)	20 (20)	33 (23)	34 (21)	0.75	30 (23)
VAS disease activity (in mm)	22 (23)	39 (26)	33 (24)	0.20	35 (25)
VAS pain (in mm)	19 (23)	35 (26)	31 (25)	0.36	32 (24)
VAS morning stiffness (in mm)	24 (26)	34 (29)	37 (28)	0.51	40 (27)
1 year follow up					
DAS	1.31 (0.78)	2.07 (0.89)	1.77 (0.90)	0.04	2.20 (0.83)
HAQ	0.38 (0.49)	0.87 (0.66)	0.81 (0.66)	0.60	0.77 (0.65)
MACTAR	63.0 (9.4)	59.2 (10.3)	60.4 (11.9)	0.54	59.7 (11.21)
MCS	53.1 (8.6)	50.5 (10.3)	50.5 (10.1)	0.97	50.4 (11.9)
PCS	48.6 (9.8)	39.9 (10.3)	43.0 (11.4)	0.10	42.6 (10.9)
VAS global (in mm)	20 (21)	33 (23)	27 (20)	0.10	33 (24)
VAS disease activity (in mm)	24 (26)	42 (29)	31 (26)	0.02	34 (27)
VAS pain (in mm)	21 (23)	38 (28)	28 (25)	0.02	28 (25)
VAS morning stiffness (in mm)	25 (26)	41 (31)	33 (27)	0.96	39 (30)
DAS-remission (DAS <1.6)	263 (68)	21 (25)	32 (41)	0.01	11 (22)

* p-value of the difference in mean scores and remission rates between arm 1 and 2. Data are presented as means and standard deviations (SD), medians and interquartile ranges (IQR), or numbers and percentages (%) when appropriate.

ACPA, anti-citrullinated protein antibody; DAS, disease activity score; HAQ, Health Assessment Questionnaire; MACTAR, McMaster-Toronto Arthritis Patients Preference Questionnaire; MCS, Mental Component Score; PSC, Physical Component Score; RA2010, rheumatoid arthritis according to the 2010 American College of Rheumatology classification criteria; VAS, visual analogue scale.

improved the most during the first 4 months in all patients.(figure 1) The mean improvement in HAQ during the first year was comparable between arm 1 and 2 (mean difference (95%CI) -0.005 (-0.3;0.2)). In the early remission group the mean HAQ score after 1 year of 0.38 was closest to the general population mean of 0.25 (compared to a mean HAQ of 0.87 in arm 1 and 0.88 in arm 2).(figure 1, table 2)

Functional ability as measured by the MACTAR, which is more sensitive to change than the HAQ, improved in all groups together with continuous improvements in mean DAS.(table 1, table 2) The mean change in MACTAR in year 1 was not significantly different between arm 1 and 2 (mean difference (95%CI) -1.1 (-5.2;3.1)). The outcomes of the OP group were comparable with those in arms 1 and 2.

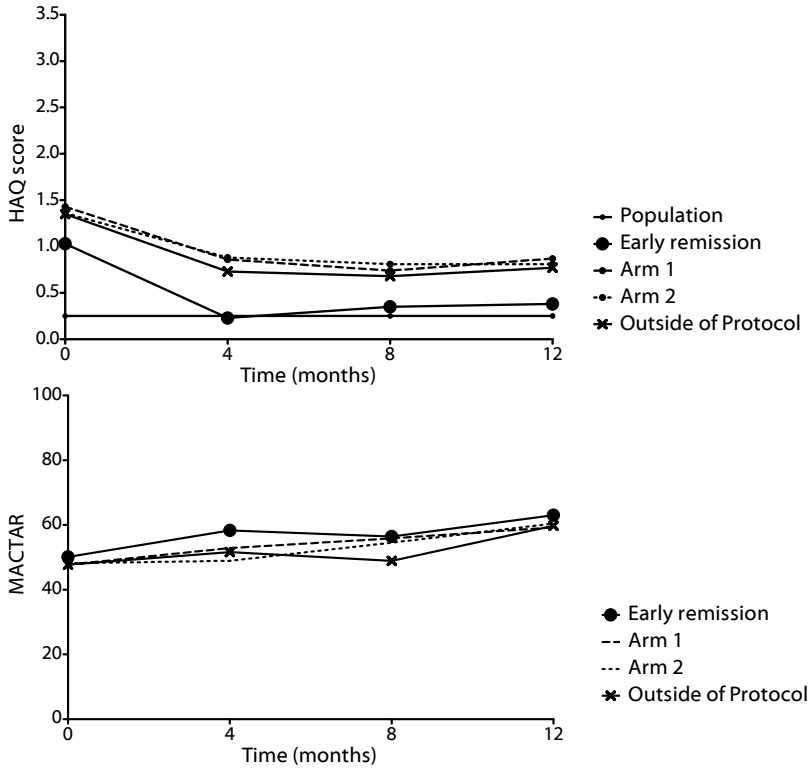

Figure 1. Functional ability as measured by the Health Assessment Questionnaire (HAQ) and the McMaster-Toronto Arthritis Patients Preference Questionnaire (MACTAR). Scores during the first year in the general population (only for HAQ), the early remission group, arm 1, arm 2 and the outside of protocol group.

Health Related Quality Of Life

At baseline, mental HRQoL measured with the mental component score (MCS) was higher than physical HRQoL measured by the physical component score (PCS) in all groups.(table

1, figure 2). Overall, the MCS at baseline was already close to the population average of 50, and improvement during the first year was minimal (table 1, figure 2), although clinically relevant in the randomization arms based on the minimal clinically important difference in component scores of 2.5-5 points (mean (SD) improvement arm 1: 3.8 (11.4), arm 2: 2.8 (10.0)). The mean improvement after 1 year was not significantly different between arm 1 and 2 (mean difference 1.0 (95%CI) -2.8;4.7). The domains in which most improvement was seen, were role emotional and social functioning.(figure 3)

For the PCS, baseline scores in all groups were below the population average of 50 (table 1, figure 2). The early remission group improved to the population average during the first 4 months of treatment and stabilized, whereas the randomization arms also improved during

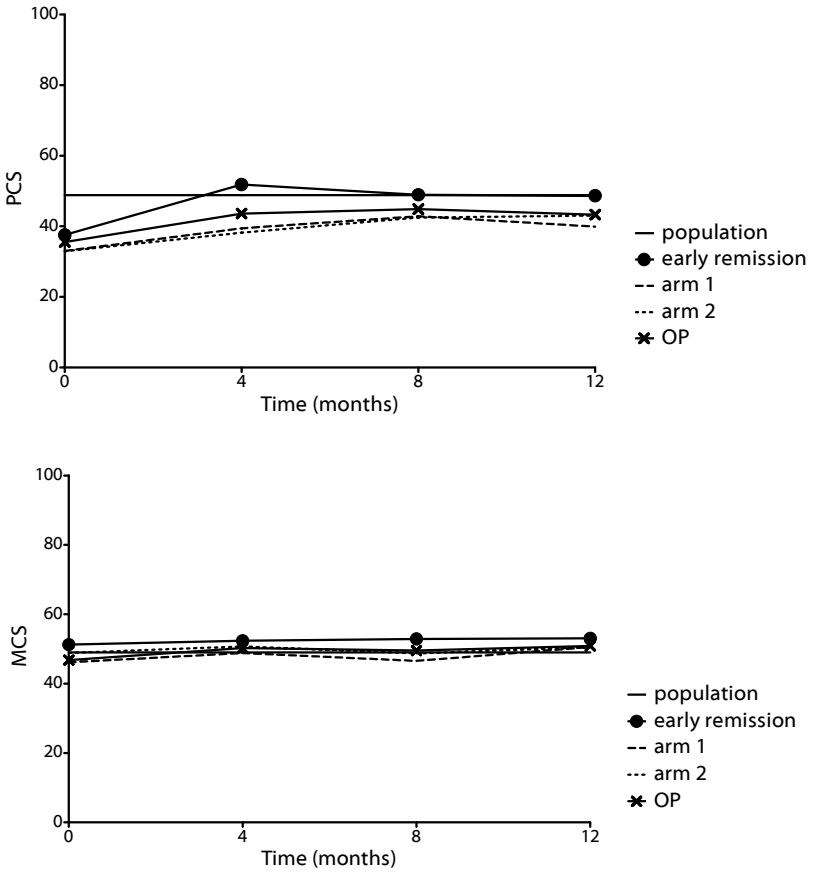

Figure 2. Summary components scores of health as measured by the Short-Form 36 (SF-36). Mental component scores (MCS) and physical component scores (PCS) are calculated from the 8 domains (physical functioning, role limitations due to physical functioning, bodily pain, general health, vitality, social functioning, role limitations due to emotional functioning and mental health) of the SF-36. Scores during the first year in the general population, the early remission group, arm 1, arm 2 and the outside of protocol group.

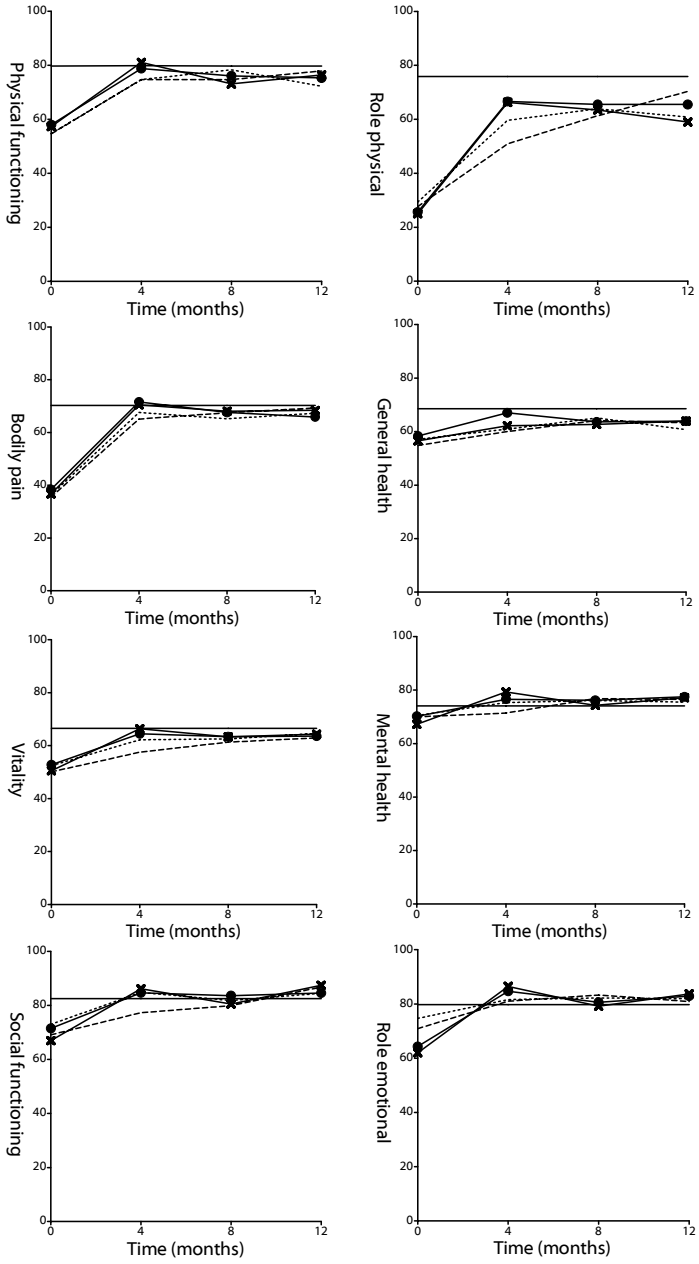

Figure 3. The 8 domains of health as measured by the Short-Form 36 (SF-36; physical functioning, role limitations due to physical functioning, bodily pain, general health, vitality, social functioning, role limitations due to emotional functioning and mental health).
Scores range from 0 (worst) to 100 (best). Scores during the first year in the general population, the early remission group, arm 1, arm 2 and the outside of protocol group.

the first 4 months and stabilized, but below the population average (table 2, figure 2). The mean (SD) improvement in 1 year was clinically relevant in all groups based on the minimal clinically important difference of 2.5-5 points: in the early remission group 11.1 (11.7), in arm 1 8.0 (10.9) and in arm 2 10.1 (12.8). The mean improvement in 1 year between patients who did and did not achieve early remission was significantly higher in patients who achieved early remission (mean difference (95%CI) -2.7 (-4.9;0.5)). There was no significant difference between arm 1 and 2 (mean difference (95%CI) -2.1 (-6.3;2.1)). The domains in which most improvement was seen, were physical functioning, role limitations due to physical functioning and bodily pain.(figure 3) Again, MCS and PCS in the OP group were comparable with those in arms 1 and 2.

Visual analogue scales

Patients who achieved early remission had at baseline and after 1 year lower VAS scores (indicating better outcomes) than the randomization arms.(table 1, table 2) Patients in arm 2 reported lower VAS scores than patients in arm 1 after 1 year.(table 2) Only for VASda there

Table 3. Association between the patient reported outcomes and remission achievement during 1 year follow up for all patients and per treatment group.

	All	Early remission	Arm 1	Arm 2	OP group
Crude beta (95%CI)					
HAQ	-	-0.31 (-0.36;-0.26)	-0.43 (-0.57;-29)	-0.45 (-0.58;-0.32)	0.18 (-0.33;-0.02)
MACTAR	7.8 (6.9;8.9)	-	-	-	-
PCS	-	6.2 (5.1;7.4)	10.2 (7.5;12.9)	8.9 (5.8;12.0)	4.5 (0.6;8.4)
MCS	0.8 (0.01;1.6)	-	-	-	-
Adjusted beta* (95%CI)					
HAQ	-	-0.30 (-0.35;-0.25)	-0.43 (-0.57;-29)	-0.45 (-0.58;-0.32)	0.17 (-0.32;-0.01)
MACTAR	8.1 (7.0;9.2)	-	-	-	-
PCS	-	6.0 (4.9;7.2)	9.9 (7.1;12.7)	9.1 (6.1;12.1)	4.2 (0.2;8.1)
MCS	0.8 (-0.01;1.7)	-	-	-	-

*Adjusted for anti-citrullinated protein antibody (ACPA) status (positive/negative), sex (male/female), disease activity score (DAS) at baseline, Tender Joint Count and Swollen Joint count.
As fixed effects were entered: time (study visit at 4 months, 8 months and 1 year) and mean baseline score of the assessed patient reported outcome. HAQ and PCS were stratified for treatment group (early remission, arm1, arm 2, outside of protocol group) because of a significant interaction between treatment group and achieving remission.
CI, confidence interval; HAQ, Health Assessment Questionnaire; MACTAR, McMaster-Toronto Arthritis Patients Preference Questionnaire; MCS, Mental Component Score; OP, outside of protocol group; PCS, Physical Component Score.

was more improvement after 1 year in arm 2 than in arm 1 (mean difference (95%CI) 13 (2;23)) and for the other VAS scores the improvement was comparable between the randomization arms (mean difference (95%CI) VASgh 7 (-2;16), VASpain 9 (-1;19) and VASms 5 (7;16). The OP group showed similar results as patients in arm 1 and 2.

Association of PROs with achieving remission (DAS <1.6)

The analyses of the HAQ and the PCS were stratified for treatment group because there was an interaction between treatment group and achieving remission. The association between HAQ and achieving remission and between PCS and achieving remission was significant in all groups during the first year of the study.(table 3) The analyses for MACTAR and MCS were not stratified. In the total study group there was a significant association between MACTAR and achieving remission. There was also a significant association between MCS and achieving remission in the total study group, but after adjustment (for ACPA status (positive/negative), sex (male/female), DAS at baseline and Tender Joint Count and Swollen Joint count at baseline, this association was no longer found.(table 3) Results were the same when we used the ACR/EULAR provisional remission definition (data not shown).

DISCUSSION

We assessed patient reported outcomes (PROs) of functional ability and health related quality of life (HRQoL) in patients with UA and early RA who were treated with the aim to achieve remission (DAS <1.6). Patients who achieved early remission after 4 months had the best PROs from baseline through the first year of the study and only in these patients PROs reached levels comparable with those measured in the general population. Patients who did not achieve early remission and were randomized to multiple DMARDs with prednisone or a combination of methotrexate with adalimumab had lower, and between arms comparable, PRO scores during the first year.

At baseline, the IMPROVED population with a mean age of 52 years scored lower on all domains of the physical HRQoL compared to healthy individuals of the Dutch population aged >70 years [12] and therefore it seems that the disease burden of early arthritis is substantial. With treatment, the component score for physical HRQoL showed a clinically relevant improvement in all groups, with the most improvement in the early remission group during the first 4 months. The mental HRQoL remained stable around the population average during the first year of treatment, which suggests that the impact of early arthritis is mainly physical. This was also shown in previous published studies.[1,16] However, improvement of physical HRQoL and HAQ to the population average in the first year after diagnosis in a remission steered treatment protocol, was not earlier reported.[1,17]

It is generally accepted that remission is the optimal treatment target in rheumatoid arthritis. Ideally, this would result in patients having no radiological joint damage progression, and no symptoms and no limitations, in other words 'normality', with functional ability and quality of life comparable to the general population. More than disease activity scores, patient reported outcomes show whether such improvement can be achieved if treatment is steered at achieving remission. The current results indicate that scores comparable with the general population can indeed be achieved, but mainly in patients who were in early remission after 4 months of initial treatment. There is possibly a two-sided relationship between early remission and better PRO scores, since patients who achieved early remission had better PRO scores at baseline than patients who did not. This indicates that maybe a predisposition to achieve remission determines the outcomes. Our results indicate that patients with a milder disease or better predisposition to achieve remission benefit from remission steered treatment because this allows them to achieve normal levels of functional ability and quality of life, which may have a significant impact on their ability to work and personal and societal costs of having (rheumatoid) arthritis.[18,19] The magnitude of the association between remission and the various PROs is actually bigger in arms 1 and 2 than in the early remission group, which had better PROs after 1 year, but also already better PROs at baseline than patients in arms 1 and 2. This suggests that regardless of baseline score, achieving remission itself is associated with PRO improvement.

One may argue that also without treatment arthritis in these patients would have regressed, with function and quality of life restored. However, previously we showed that patients who achieved remission were in majority ACPA positive, which makes spontaneous remission less likely.[5]

Although after 1 year significantly more patients in arm 2 achieved remission than in arm 1, we found no significant differences in improvement of functional ability, HRQoL and VAS results between both arms. Only VAS disease activity, as estimated by the patient, improved more in arm 2 than in arm 1. Despite continued treatment adjustments targeted at remission, remission percentages in both arms remained lower than in the early remission group. Possibly as a consequence also functional ability and HRQoL in the physical domain did not achieve the same levels as the early remission group. In particular HAQ was higher in the randomization arms than in the early remission group and physical HRQoL did not reach levels found in the general population. Although we found that PROs were associated with achieving remission and significantly more patients in arm 2 achieved remission after 1 year than in arm 1, we found no significant differences in improvement of functional ability and HRQoL between both arms. Only improvement in VAS disease activity was significantly better in patients of arm 2 compared to patients in arm 1, which can be explained by a significantly lower mean DAS in arm 2 and it may also be related to higher patient expectations associated with earlier introduction of subcutaneous TNF-inhibitor, adalimumab, in this treatment arm.[20,21] Overall, disease activity was well suppressed in both arms which may explain why we

have found no differences in improvement in HAQ and HRQoL. The actual DAS, rather than having a score just above or below the threshold of remission, may be the main determinant of PROs. The patients in the OP group have similar results as patients in arm 1 and 2 which can be explained by the comparable response on initial treatment.

In conclusion, there is an association between achieving remission and having better functional ability and health related quality of life and other PROs in patients with early (rheumatoid) arthritis, which may in part be bidirectional. Patients who achieve early remission improve and remain at levels of the general population. This supports the idea that early remission steered treatment could result in complete suppression of symptoms with normal functioning and may prevent chronic deterioration also in patient reported outcomes.

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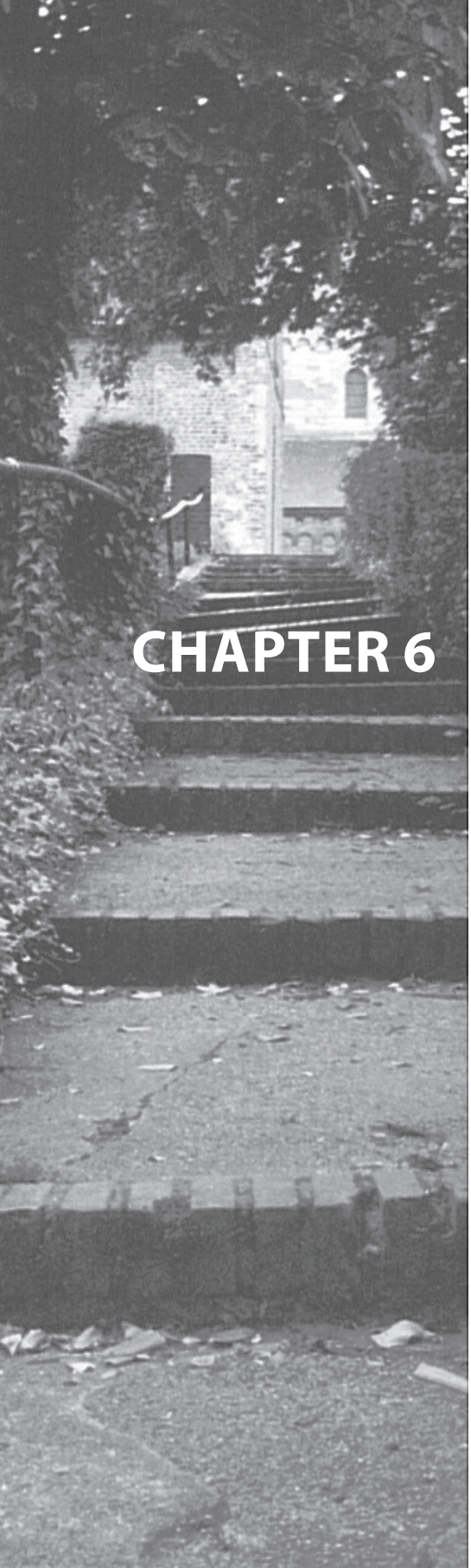

CHAPTER 6

Determinants of drug free remission in patients with early rheumatoid or undifferentiated arthritis after one year of remission steered treatment

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Submitted

ABSTRACT

Objective

To assess if baseline characteristics in patients with undifferentiated or early rheumatoid arthritis affect the possibility to achieve drug free remission after one year (DFR_{1year}) of early remission induction therapy.

Methods

We included 375 patients participating in the IMPROVED study, who achieved remission (DAS<1.6) after four months (early remission) and were by protocol able to achieve DFR_{1year}. Having started with methotrexate (MTX) plus prednisone, patients tapered prednisone to zero after 4 months. After 8 months, those still in remission tapered MTX to zero, while those not restarted prednisone. Characteristics of patients achieving and not achieving DFR_{1year} were compared. Logistic regression was performed to identify predictors of DFR_{1year}.

Results

After one year, 119 patients (32%) were in DFR. Presence of Rheumatoid Factor (RF), fulfilling the 2010 criteria for RA and a low tender joint count were associated with achieving $DFR_{1year,}$ whereas presence of ACPA was not. None of the baseline characteristics were independently associated with $DFR_{1year.}$ DFR_{1year} was sustained for 4 months in 65% patients. ACPA positive patients less often had sustained DFR than ACPA negative patients (58% versus 80%, p=0.013).

Conclusions

After 1 year of remission steered treatment, 32% of the patients who had achieved early remission after 4 months, were able to taper medication and achieved DFR. Neither presence of ACPA nor other baseline characteristics were independently associated with achieving DFR after 1 year but in ACPA positive patients DFR was less often sustained.

INTRODUCTION

With the current treatment strategies, remission has become a realistic goal in patients with rheumatoid arthritis (RA).[1-3] It remains to be seen whether achieving drug free remission (DFR) after tapering medication is also a realistic goal. In recent cohort studies and clinical trials in patients with RA, DFR rates vary between 17 and 29% [4-6] and DFR was sustained for 1-4 years in 9-16%.[4-7] Previously reported independent predictors for sustained DFR are absence of Anti-Citrullinated Protein Antibodies (ACPA), Rheumatoid Factor (RF) and shared epitope, short symptom duration and low disease activity until remission.[6,7]

In the IMPROVED study, patients with recent onset RA or undifferentiated arthritis (UA) clinically suspected for RA received initial treatment with a combination of MTX and a tapered high dose of prednisone. If remission (DAS <1.6) was achieved after 4 months, medication was stepwise tapered until DFR could be achieved already after 1 year (DFR_{1year}).

We previously reported that 61% of the patients achieved early remission after 4 months. Surprisingly, these patients were more often ACPA positive than the patients who did not achieve early remission.[8] Here, we aimed to assess whether ACPA status also influenced the likelihood to achieve DFR_{1year} and to identify possible other determinants of achieving DFR_{1year}.

METHODS

Patients, study design and outcomes

IMPROVED is a multi-center clinical trial in 122 patients with undifferentiated arthritis (UA) and 479 patients with recent onset rheumatoid arthritis (RA, 2010 criteria), treated according to a tight controlled, remission (DAS <1.6[9]) steered protocol. Details on in- and exclusion criteria were previously published.[10] Initially, all patients were treated with MTX 25 mg/week plus prednisone 60 mg/day tapered in 7 weeks to 7.5 mg/day, continued up to 4 months. Patients not in remission after 4 months by protocol could not achieve DFR_{1year} because they had to take additional treatment steps before tapering was possible, and thus were left out of the current analysis. Patients who achieved remission after 4 months (early remission) first tapered prednisone to zero in 4 weeks and, if still in remission after 8 months, also tapered MTX to zero in 2 months. Patients who lost remission while still on MTX restarted prednisone and patients who already discontinued MTX restarted MTX. DFR_{1year} was defined as having a DAS<1.6 from 4 months to 1 year while both prednisone and methotrexate (MTX) were subsequently tapered and stopped. Because DFR_{1year} was only achieved about 2 months before the end of year 1, we included 16 months follow up data to see if DFR could be sustained. Details on study protocol and scoring methods were previously published.[11]

Statistical analysis

Clinical, radiological and laboratory variables during the first year were compared between patients achieving and not achieving DFR_{1year} using the students T test, Mann Whitney U test and Chi Square test. All available baseline clinical, demographic and laboratory characteristics were entered as covariates in univariate logistic regression analyses, with DFR_{1year} as binomial dependent variable. Using a significance level of 0.10, univariate significant variables were entered in a multivariate model to identify independent predictors.

RESULTS

After 4 months, 375 (61%) patients achieved early remission, of which 291 (78%) fulfilled the 2010 classification criteria for RA. Compared to patients not in early remission, patients in early remission had lower mean baseline DAS and HAQ levels, more were ACPA positive and fewer were female.[8] After one year, 119 (32%) patients were in DFR and 245 (65%) were not, although 138 (56%) of those were in remission but on medication. Eleven patients had insufficient data. Whether patients fulfilled the 1987 [12] and/or the 2010 classification criteria for RA [10] did not significantly affect the DFR_{1year} rate (DFR_{1year} was achieved by 51 (28%) patients who fulfilled both classification criteria, 33 (34%) who fulfilled the 2010 but not the 1987 criteria and 21 (37%) who fulfilled neither (p=0.4)). Similar proportions of patients in DFR_{1year} and not in DFR_{1year} were ACPA positive (66 (55%) versus 150 (61%) respectively, p=0.2). There were no differences in baseline DAS, symptom duration and percentage of females between patients in and not in $DFR_{1year.}$ Patients in DFR_{1year} were more often RF negative, and after 4 months as well as after 1 year, they had lower mean DAS and HAQ values than patients not in $DFR_{1year.}$ (table 1)

Results of the univariate regression analyses are shown in table 2. Baseline DAS and HAQ values, ACPA status, age, male sex and symptom duration were not associated with achieving DFR_{1year}. RF positivity, high baseline TJC and fulfilling the 2010 criteria for RA were predictive for less often achieving DFR_{1year}. In a multivariate regression model none of these variables were independently predictive for less often achieving DFR_{1year} (adjusted OR (95%CI) RF positivity 0.6 (0.4-1.1), baseline TJC 0.9 (0.9-1.0), fulfilling the 2010 criteria for RA 0.9 (0.5-1.8)). After leaving out the least significant variable, fulfilling the 2010 criteria for RA (p=0.8), odds ratio's did not change importantly, although RF positivity adjusted for TJC was significantly predictive for less often achieving DFR_{1year} (data not shown).

Seventy seven (65%) patients in DFR_{1year} were still in DFR after 16 months (DFR_{16mo}), 36 (30%) were not and 6 patients had missing data. Those who lost remission were more often ACPA positive than those who sustained DFR (26 (72%) versus 36 (47%), p=0.01), and ACPA positive patients less often sustained remission than ACPA negative patients (36 (58%) versus 40 (80%), p=0.013). Regardless of achieving DFR_{1year}, 107 (29%) patients achieved DFR_{16mo}. Patients in DFR_{16mo} were less often ACPA positive than those not in DFR_{16mo} (47 (44%) versus 159 (67%), p<0.001).(figure 1)

Table 1: Baseline characteristics and clinical outcomes of patients who are and are not in drug free remission after one year.

	DFR_{1year} N= 119	No DFR_{1year} N= 245	p-value
Baseline			
DAS	2.9±0.9	3.0±0.8	0.3
Swollen joint count	4 (2-10)	5 (3-9)	0.2
Tender joint count	5 (3-8)	6 (4-8)	0.1
VAS global health, mm	41±25	43±24	0.3
ESR mm/hr	21 (11-36)	24 (10-38)	0.5
HAQ	1.0±0.7	1.0±0.6	0.5
Age, years	52±13	51±14	0.5
Symptom duration, weeks	16 (8-30)	17 (9-32)	0.4
Female	67 (56)	158 (64)	0.1
RF positive	60 (50)	152 (62)	0.03
ACPA positive	66 (55)	150 (61)	0.2
Diagnosis RA(2010)	87 (74)	196 (80)	0.1
Diagnosis RA(1987)	61 (51)	138 (56)	0.4
SHS total score	0 (0-1)	0 (0-0)	0.08
Erosive	20 (17)	31 (13)	0.3
4 months follow up			
DAS	0.8±0.4	1.0±0.4	<0.001
Swollen joint count	0 (0-0)	0 (0-0)	0.3
Tender joint count	0 (0-1)	0 (0-1)	0.07
VAS global health, mm	12±14	15±13	0.1
ESR mm/hr	6 (2-11)	7 (4-13)	0.08
HAQ	0.2±0.3	0.3±0.3	0.006
ACR/EULAR remission	57 (48)	86 (35)	0.006
1 year follow up			
DAS	0.9±0.4	1.5±0.8	<0.001
Swollen joint count	0 (0-0)	0 (0-2)	<0.001
Tender joint count	0 (0-0.5)	1 (0-3)	<0.001
VAS global health, mm	12±15	25±22	<0.001
ESR mm/hr	6 (3-11)	9 (4-18)	0.01
HAQ	0.2±0.3	0.5±0.5	<0.001
DAS-remission	119 (100)	138 (56)	<0.001
ACR/EULAR remission	64 (54)	54 (22)	<0.001

Data are presented as means ± standard deviations (SD), medians and interquartile ranges (IQR), or numbers and percentages (%) when appropriate. Eleven patients had missing data after 1 year.
ACPA, anti-citrullinated protein antibodies; ACR/EULAR remission, remission according to the Boolean based ACR/EULAR provisional remission definition, based on 44 joint counts; $DFR_{1year,}$ drug free remission defined as DAS<1.6 and all medication tapered after 1 year; DAS, disease activity score; Erosive, number of patients having one or more erosions; DAS-remission, defined as a DAS<1.6; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; RA(2010), Rheumatoid Arthritis according to the 2010 ACR/EULAR classification criteria, RA(1987), RA according to the 1987 ACR classification criteria; SHS harp-van der Heijde score; RF, rheumatoid factor;VAS, visual analogue scale.

Table 2: Univariate logistic regression analyses with drug free remission after 1 year (yes/no) as dependent variable.

Baseline characteristics	Crude OR	95%CI	p-value
Age, years	1.0	0.99-1.0	0.3
Male sex	1.4	0.9-2.2	0.13
DAS	0.8	0.6-1.0	0.10
HAQ	0.9	0.6-1.2	0.5
TJC	0.9	0.9-1.0	0.08
SJC	0.99	0.95-1.0	0.6
ESR, mm/hr	0.996	0.99-1.0	0.4
Symptom duration, weeks	0.997	0.99-1.0	0.6
ACPA positivity	0.7	0.5-1.2	0.2
RF positivity	0.6	0.4-0.96	0.03
Diagnosis RA(2010)	0.6	0.4-1.1	0.099

ACPA, anti-citrullinated protein antibodies; 95% CI, 95% confidence interval; DAS, baseline disease activity score; ESR, baseline erythrocyte sedimentation rate (mm/hr); HAQ, baseline health assessment questionnaire; OR, odds ratio; RA(2010), rheumatoid arthritis according to the 2010 ACR/EULAR classification criteria; RF, rheumatoid factor; SJC, baseline swollen joint count; TJC, baseline tender joint count.

DISCUSSION

In the IMPROVED study, 32% of the early arthritis patients who had achieved remission after 4 months, were able to maintain remission and taper all medication to drug free remission after 1 year (DFR_{1year}), regardless of fulfilling the 1987 and/or 2010 classification criteria for RA at study entrance. Baseline characteristics in the past associated with chronic and/or progressive disease, such as a positive RF and fulfilling criteria for RA, were associated with less often achieving DFR_{1year}, although not independently of each other. Also a high tender joint count at baseline was, non-independently, associated with less often achieving DFR_{1year}. ACPA status and symptom duration were not associated with DFR_{1year}. In 65% of patients in DFR_{1year}, DFR was sustained for 4 more months. Although DFR was achieved in ACPA positive patients as often as in ACPA negative patients, ACPA positive patients less often sustained in DFR than ACPA negative patients.

To our knowledge, IMPROVED is the first study in which DFR was a treatment goal. A DFR rate of 32% after 1 year is probably high, although 29% of the total IMPROVED population did not achieve early remission after 4 months and by protocol were not able to achieve DFR already after 1 year.

Given the fact that we included both RA and UA patients, clinically suspected to have RA but not fulfilling the criteria, we may have included and treated patients who might have remitted spontaneously. This was a reason why we introduced a rapid drug tapering scheme in our protocol. However, if the 32% mainly represented non-chronic types of arthritis, one

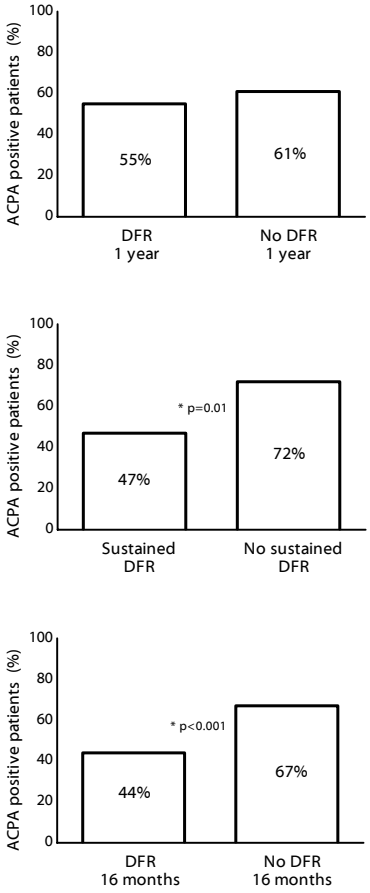

Figure 1: Percentages ACPA positive patients achieving drug free remission after 1 year versus not, sustaining drug free remission up to 16 months versus not and achieving drug free remission after 16 months versus not.
ACPA, anti-citrullinated protein antibodies; DFR 1 year, drug free remission after 1 year; DFR 16 months, patients in DFR after 16 months, regardless of being in DFR after 1 year; Sustained DFR, patients in DFR after 1 year and after 16 months.

would expect that these patients more often were auto-antibody negative, possibly had shorter disease duration or less often fulfilled the criteria sets for RA than patients not achieving DFR, which was not the case.

Interestingly, presence of ACPA was not associated with less DFR_{1year}. Previously we reported that presence of ACPA was associated with achieving more remission after 4 months in the IMPROVED study,[8] which was in contrast with previous data indicating that presence of ACPA is associated with a less favorable disease course.[13,14] In a study comparing DFR in the Leiden Early Arthritis Clinic and the BeSt study, absence rather than presence of ACPA was an independent predictor of sustained DFR.[7] That ACPA positive patients achieve DFR_{1year} in

similar numbers as ACPA negative patients may be explained both by the initial combination with MTX and prednisone and the early remission steered treatment in the IMPROVED study.

However, after treatment was stopped 30% of patients lost remission and had to restart medication within 4 months after achieving DFR, and ACPA positive patients more often lost DFR than ACPA negative patients. This suggests that compared to ACPA negative patients, ACPA positive patients have a similar likelihood of achieving and maintaining remission, even while medication is tapered. But after having successfully tapered and discontinued medication, ACPA positive patients show more relapses in disease activity in the next 4 months, and this may even increase with follow up. Reasons why sustained DFR was achieved less often in ACPA positive patients may be that we have tapered medication too soon or too fast or have not used the optimal initial treatment within the optimal time frame. In the future we will also be able to see which patients who did not achieved early remission after 4 months, may achieve late DFR in the randomization arms and whether this is sustained over time.

In conclusion, 32% of patients with early arthritis who achieved remission after 4 months of initial combination therapy can taper medication until DFR is achieved after one year. Achieving DFR is possible regardless of ACPA status or other baseline disease characteristics, but DFR is sustained less often in ACPA positive than in ACPA negative patients.

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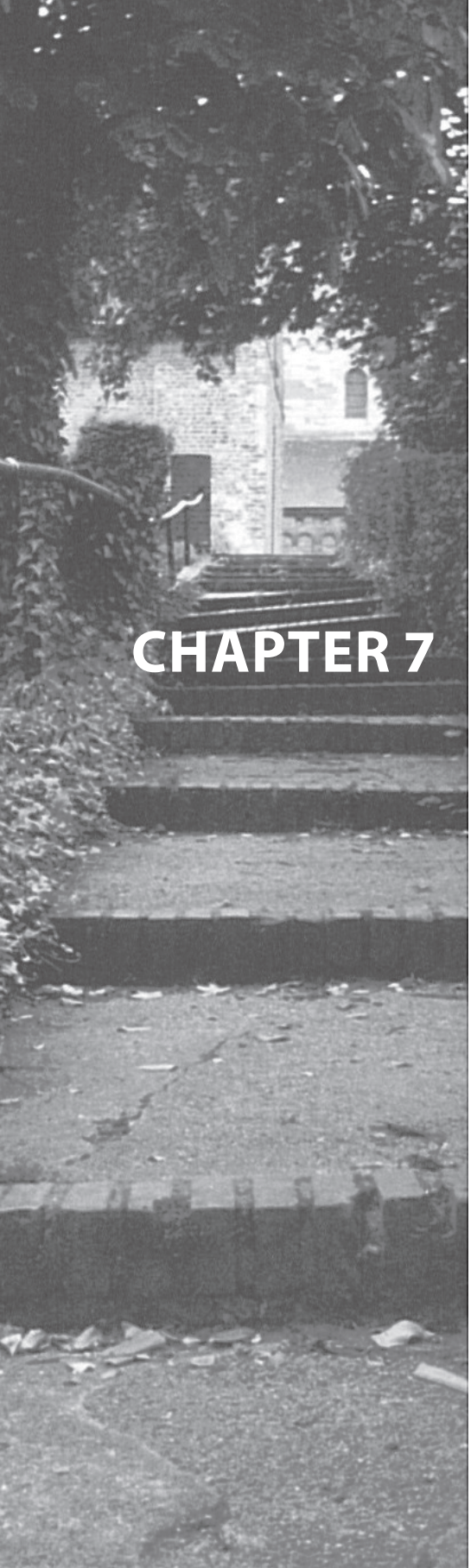

CHAPTER 7

The relationship between disease activity and depressive symptoms severity and optimism – results from the IMPROVED study

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ABSTRACT

Objective

To assess depressive symptoms severity and dispositional optimism in patients with recent onset arthritis, both before and after 4 months treatment.

Methods

Two-hundred-twenty-two patients with recent onset RA and undifferentiated arthritis (UA) in the IMPROVED study filled out the Beck Depression Inventory (BDI-II) to assess depressive symptoms severity and the Life Orientation Test Revised (LOT-R) to measure optimism before and after 4 months of treatment. All patients were treated with methotrexate (MTX) 25 mg/week and prednisone 60 mg/day (tapered to 7.5 mg/day in seven weeks). Linear regression analysis was used to assess the association between the Disease Activity Score (DAS) and its components (Tender Joint Count, Visual Analogue Scale (VAS) Global Health, Swollen Joint Count and Erythrocyte Sedimentation Rate (ESR)) with the BDI-II an LOT-R scores.

Results

In general, depressive symptoms were mild. The DAS was an independent predictor of depressive symptoms scores both at baseline and after 4 months follow-up, in particular Tender Joint Count and VAS Global Health. Disease activity was not associated with the level of optimism. Nevertheless, patients who achieved clinical remission improved significantly more in both depression score and optimism score than patients who did not.

Conclusions

Patients with early arthritis report improvement in depressive symptoms and optimism with improvement in disease activity and achieving clinical remission. Depression scores are associated with pain and unwell being but not with swollen joint counts and inflammatory parameters.

INTRODUCTION

Depressive symptoms are more common in patients with rheumatoid arthritis (RA) compared to healthy individuals.[1-4] The etiology of the association between RA and depressive symptoms is poorly understood.[2] Pain and disability may negatively affect mood (and vice versa), but inflammatory processes itself may also play a role in inducing depressive symptoms.[5,6] Suppression of disease activity might improve depressive symptoms.[3] However, anti-rheumatic treatment with oral corticosteroids, in particular in higher dosages, may also induce psychiatric disorders including depression, anxiety, delirium and (hypo)mania.[7-10] To investigate the relationship between disease activity and mood, we assessed levels of depressive symptoms and dispositional optimism [11] in patients with recent onset arthritis who were treated with methotrexate and a high tapered dose of prednisone with the aim to induce clinical remission in the IMPROVED study.

PATIENTS AND METHODS

Study design

The IMPROVED study is a multicenter investigator driven clinical trial among patients with recent onset arthritis, designed and conducted by rheumatologists in 12 cooperating hospitals in the Western part of the Netherlands. The Medical Ethics Committee of each participating center approved the study protocol and all patients gave written informed consent. Patients with undifferentiated arthritis (UA) and recent onset RA were included. Recent onset RA was defined according to the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 2010 classification criteria [12] with a duration of symptoms ≤2 years. UA patients had at least 1 joint clinically assessed as 'arthritis' and at least 1 other tender joint, in the opinion of the rheumatologist clinically suspected to represent early RA but not fulfilling the 2010 ACR/EULAR criteria. All patients were recruited between March 2007 and September 2010, were at least 18 years old, disease modifying anti-rheumatic drug (DMARD) naïve and had a Disease Activity Score (DAS) ≥1.6. Exclusion criteria included pregnancy, malignancy within the last five years, bone marrow hypoplasia, elevated liver enzyme levels (AST and/or ALT >3 times normal value), serum creatinine level >150 umol/l or estimated creatinine clearance of <75%, uncontrolled diabetes mellitus, uncontrolled hypertension, heart failure (NYHA class III/IV), alcohol or drug abuse, serious infections in the previous 3 months or chronic infectious disease, opportunistic infections within previous 2 months, active or latent hepatitis B, HIV infection or AIDS, lymphoproliferative diseases and multiple sclerosis.

All patients received initial treatment in the first 4 months with methotrexate 25 mg/week and prednisone 60 mg/day, tapered to 7.5 mg/day in 7 weeks.

Outcomes

At baseline and after 4 months a trained assessor performed a full joint evaluation and calculated a DAS. Patients were asked to fill out a Visual Analogue Scale (VAS) for global wellbeing, the Health Assessment Questionnaire (HAQ) [14], and questionnaires on educational level, job-participation and productivity. Separate informed consent was obtained for additional questionnaires, the Beck Depression Inventory II (BDI-II) and the Life Orientation Test Revised (LOT-R).[15,16]

The BDI-II is a 21-item questionnaire to assess depressive symptoms severity according to the diagnostic criteria as stated by the DSM-IV. It is scored as the sum of scores (0-3). Missing values e.g. unanswered questions (12 questions in the baseline questionnaire, 15 questions in the 4-month questionnaire) were replaced with zero. This is the neutral answer in all questions; in case of the question about 'sadness', 0 means 'I don't feel sad'. Patients with a total score of 0-13 are defined as having minimal depressive symptoms, a score of 14-19 denotes mild depressive symptoms, 20-28 moderate depressive symptoms and 29-63 severe depressive symptoms.[15]

Dispositional optimism was assessed by using the Life Orientation Test - Revised (LOT-R). The LOT-R is a 10-item continuous scale to measure optimism.[16] The questionnaire consists of 6 score items and 4 filler items, answered on a 0-4 Likert scale (0 strongly disagree, 4 strongly agree). Three items are keyed in a positive direction and three in a negative direction, and negatively worded items (i.e. items 3, 7 and 9) are reversely coded. The total score is calculated as the sum of the score items (i.e. items 1, 3, 4, 7, 9, and 10), with a range between 0 and 24 with higher scores indicating greater optimism. Low dispositional optimism has previously been defined as a total score <12 (often yielding ±20% of the subjects with the lowest scores).[17] Missing values were replaced with the rounded mean of the remaining score items, if at least 4 of the 6 score items were filled out.[18] Previously, college-students in the United States scored a mean (standard deviation (SD)) LOT-R score of 14.3 (4.3); patients after bypass surgery scored 15.2 (4.1).[16]

Statistical analyses

Comparison between participants of IMPROVED who filled out the BDI-II and LOT-R and participants who did not, were analyzed using the independent t-test, the Wilcoxon rank sum tests and the Chi-squared test at the 5% level. Linear regression analysis was used to assess the relationship between DAS scores and depressive symptoms severity scores, both at baseline and at 4 months follow-up. We adjusted for age, gender and alcohol use (yes/no), because these characteristics are known to be related to depressive symptoms as well as (changes in) disease activity. Given the possible association between the questionnaire outcomes on the one hand and marital status (not married and living alone, not married and living together, married, divorced, widow(er)), having children (yes/no), level of education (highest level of education; primary school, secondary education, vocational education or university), employment (yes/no) and tobacco use (yes/no) on the other hand, the analyses were repeated with these

covariates included in the model. The analyses to assess the relationship at follow-up were also adjusted for baseline disease activity and baseline questionnaire scores. Subsequently, separate analyses were done for the components of the DAS: Tender Joint Count and patients' sense of general wellbeing, measured with a VAS as subjective components, and Swollen Joint Count and Erythrocyte Sedimentation Rate (ESR) as objective components. Univariate and multivariate analyses were done separately for Tender Joint Count and Swollen Joint count because of collinearity. The regression analyses were also done for the LOT-R questionnaire.

Finally, questionnaire outcomes were compared at baseline and after 4 months using the paired t-test at the 5% level. Differences in change scores of the BDI-II and LOT-R between patients who achieved remission (defined as a DAS<1.6 [19]) and those who did not were evaluated with an ANCOVA model with remission achievement (yes/no) as factor and the baseline values of BDI-II or LOT-R as a covariate. Statistical analyses were conducted with SPSS for Windows version 17.0 (SPSS Inc., Chicago, Ill).

RESULTS

Characteristics of participants

Six-hundred-and-ten patients were included in the IMPROVED study of whom 222 patients gave informed consent to fill out the questionnaires and filled out at least one of the questionnaires at baseline or after 4 months. Of these, 211 patients completed the LOT-R and 215 patients the BDI-II both at baseline and follow-up. Patient characteristics are presented in table 1. Among patients who filled out the BDI-II and optimism questionnaires, a higher percentage was ACPA-positive (p=0.050) and had children (p=0.03), compared to those who did not fill out the questionnaires (table 1).

Eight of 610 patients (1.3%) reported having a depression in their medical history. None of these patients reported having ongoing symptoms, 3 reported using antidepressants and 2 patients reported being under care of a psychologist/psychiatrist. Seven other patients reported using antidepressants without mentioning having a depression in their medical history.

Depressive symptoms severity over time

Disease activity was at both time points independently positively associated with depressive symptoms severity (baseline beta 0.26, p<0.001 and 4 months beta 0.31, p<0.001). The results did not change after adjustment for marital status, having children, level of education, employment and tobacco use. At baseline the DAS-component VAS for global well-being and after 4 months both Tender Joint Count and VAS for global wellbeing, but not Swollen Joint Count or ESR, were independently associated with BDI-II score (table 2).

After 4 months of treatment with methotrexate and prednisone, there was a significant decrease in mean (SD) BDI-II score in the entire group from 8.5 (7.7) at baseline to 7.0 (7.2)

Table 1. Baseline characteristics of patients who filled out BDI-II and optimism questionnaires compared to patients who did not.

Baseline	Patients who filled out the BDI-II and LOT-R (n=222)*	Other IMPROVED patients (n=388)	P value
Socio-demographics			
Age (years)	51.4 ± 12.5	52.2 ± 14.7	0.45
Female sex	157 (71)	257 (66)	0.25
Married	143 (64)	237 (61)	0.40
Children	184 (83)	300 (77)	0.03
Higher education	73 (33)	177 (29)	0.12
Working	121 (55)	199 (51)	0.10
Disease characteristics			
DAS	3.2 ± 0.9	3.2 ± 0.9	0.51
Duration of symptoms (weeks)	18 (9-36)	18 (9-32)	0.49
ACPA positive	134 (60)	199 (51)	0.050
ESR	24 (11-37)	25 (11-41)	0.21
Tender Joint count	6 (4-9)	6 (4-9)	0.96
Swollen joint count	6 (3-10)	5 (2-10)	0.38
VAS global health	44 ± 24	47 ± 23	0.10
HAQ	1.1 ± 0.7	1.2 ± 0.7	0.28
BDI-II	8.5 ± 7.7	-	-
LOT-R	16.7 ± 4.0	-	-
Health related factors			
Smoking	63 (28)	114 (29)	0.79
Alcohol	130 (59)	232 (60)	0.67

*Data of patients who filled out at least one of the questionnaires, at one of the time points. Data are presented as means ± standard deviations (SD), medians and interquartile ranges (IQR), or numbers and percentages (%) when appropriate.
ACPA, Anti-Citrullinated Protein Antibodies; BDI-II, Beck Depression Inventory II; DAS, Disease Activity Score; ESR, Erythrocyte Sedimentation Rate; HAQ, Health Assessment Questionnaire; LOT-R, Life Orientation Test Revised; VAS, Visual Analogue Scale.

(95%CI -2.3;-0.6, p=0.001). Depressive symptoms after treatment were minimal, only 21/215 (9.8%) had mild depressive symptoms (BDI-II score 14-19), 11/215 (5.1%) had moderate (BDI-II score 20-28) and 5/215 patients (2.3%) had severe depressive symptoms (BDI-II>29). After four months, 138 (66%) patients had achieved clinical remission, with a mean (SD) DAS of 0.9 (0.4). BDI-II scores after 4 months were significantly decreased in patients who achieved remission (mean (SD) 6.9 (6.4) to 4.8 (5.0), 95%CI -3.1;-1.2, p<0.001), but not in patients who did not achieve remission (mean (SD) 11.2 (8.9) to 11.0 (8.7), 95%CI -1.96;1.6, p=0.83). In patients who did achieve remission the mean change in BDI-II was 4.0 (SE 0.8) points lower than in patients who did not (p<0.001).(figure 1)

Table 2. The association between DAS-components and BDI-II, separately for tender joint count and swollen joint count.

	Crude beta (p-value)	Adjusted beta (p-value)
Baseline		
Tender Joint Count	0.27 (<0.001)	0.12 (0.08)[1]
ESR	-0.004 (0.96)	0.02 (0.75)[1]
VAS	0.33 (<0.001)	0.31 (<0.001)[1]
4 months follow up		
Tender Joint Count	0.41 (<0.001)	0.14 (0.04)[2]
ESR	0.04 (0.53)	0.04 (0.57)[2]
VAS	0.47 (<0.001)	0.30 (<0.001)[2]
Baseline		
Swollen Joint Count	0.11 (0.27)	0.04 (0.57)[1]
ESR	-0.004 (0.96)	0.01 (0.85)[1]
VAS	0.33 (<0.001)	0.34 (<0.001)[1]
4 months follow up		
Swollen Joint Count	0.14 (0.04)	0.04 (0.79)[2]
ESR	0.04 (0.53)	0.04 (0.54)[2]
VAS	0.47 (<0.001)	0.35 (<0.001)[2]

1.Beta adjusted for: age, gender, alcohol consumption yes/no. 2. Beta adjusted for: age, gender, alcohol consumption yes/no, Disease Activity Score at baseline, outcome BDI-II at baseline.
ESR, Erythrocyte Sedimentation Rate; VAS, Visual Analogue Scale global health.

Optimism over time

At baseline, disease activity was not associated with optimism scores as assessed with the LOT-R (beta 0.001, p=0.99). After 4 months DAS score and LOT-R score (beta -0.14, p=0.02) were inversely associated, but this association disappeared after adjustment for age, gender, marital status, having children, level of education, employment and alcohol and tobacco use (beta 0.02, p=0.79).

At baseline, the optimism score was 16.7 and after 4 months 16.5 (95%CI -0.7;0.3, p=0.42) in the entire group. The LOT-R scores for optimism and BDI-II scores for depressive symptoms severity were significantly associated both at baseline and after 4 months (beta -0.51 (p<0.001) at baseline and beta -0.44 (p<0.001) after 4 months). Patients with higher optimism scores had less depressive symptoms.

Of the 211 patients who filled out the questionnaire twice, 138 (65.7%) achieved remission after 4 months (mean (SD) DAS 0.9 (0.4)). LOT-R scores remained stable from baseline to 4 months, whether remission was achieved (mean (SD) 17.0 (4.1) to 17.1 (3.5), 95%CI -0.4;0.7, p=0.08) or not (16 (3.9) to 15.2 (3.7), 95%CI -1.6;0.1, p=0.68). Yet, the mean change in LOT-R was 1.4 (SE 0.4) points higher than in the patients who did not achieve remission (p=0.001).(figure 1) In all patients, LOT-R scores were above the cut-off of 12.

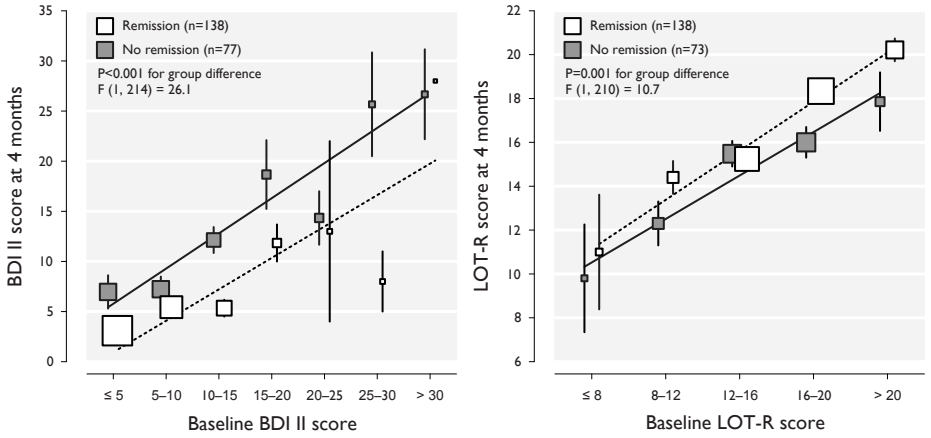

Figure 1. Univariate regression lines of patients with and without remission.
The size of each square is proportional to the number of patients. P-values by analysis of covariance for the group difference, while adjusting for baseline values. Continuous values were used throughout the statistical analyses; categorization of baseline BDI-II and optimism scores was done for visualization purposes only.
BDI-II, Beck Depression Inventory II; LOT-R, Life Orientation Test Revised

DISCUSSION

In patients with recent onset rheumatoid and undifferentiated arthritis disease activity showed a relationship with depressive symptoms severity. In patients who achieved clinical remission after 4 months of treatment with methotrexate and prednisone, both depression scores and optimism scores improved significantly more compared to patients who did not achieve remission.

Our intention was to monitor possible mood changes that might occur during treatment with the high tapered dose of prednisone used to try to induce remission of early arthritis in our patients. Depression, as well as mania, could be induced by corticosteroids.[10] Although we do not have a control group to compare the effect of corticosteroids, the finding that none of the patients in the IMPROVED study expressed extreme values on either the depression or the optimism questionnaire, makes it unlikely that prednisone greatly influenced depressive symptoms or optimism. More likely, the changes in mood scores that we saw are related to a previously described association between rheumatoid arthritis and depression.[4] The patients in the current study had early and relatively mild arthritis and did not carry the extra burden of joint destruction and the comorbidity of advanced rheumatoid arthritis, which may explain why only few patients had more than minimal depressive symptoms.

It has previously been hypothesized that the occurrence of depressive symptoms in RA is related to inflammatory processes and immune activation. This was based on the finding that in patients with depression, increased serum levels of cytokines IL-1, IL-6 and TNF-alpha

were found.[5,6] In our study, it appears that the depressive symptoms depended mostly on the presence and extend of joint tenderness on examination and reported global wellbeing as measured with a Visual Analogue Scale rather than on joint swelling and increased erythrocyte sedimentation rate as signs of inflammation. Therefore our results do not support the hypothesis on inflammation and depression but point into the direction of a relation between mood and pain.

This relation may be bidirectional, as already at baseline patients with more severe pain had more severe depressive symptoms, which is consistent with previous findings [20] while patients who have more severe depressive symptoms may also be more susceptible for and report more pain.[21-23] Even if inflammation is well suppressed with prednisone and methotrexate, residual or non-inflammatory pain can prevent that the patient will be assessed as being in remission. This may explain why patients who did not achieve remission after 4 months had higher depression scores. And this in turn may be related to the fact that patients who did not achieve remission had significantly higher depression scores at baseline than patients who did achieve remission. Since all patients knew that the treatment goal in the IMPROVED trial was to achieve remission, after which medication would be tapered and finally discontinued, it may be that not achieving remission and therefore having to intensify medication, also influenced feelings of depression.[3]

Changes in disease activity or arthritic symptoms in general were not related to level of optimism as measured with the LOT-R questionnaire, which did not significantly change over time. This is possibly related to the fact that optimism levels at baseline were above the cut-off for low optimism in the majority of our patients. Also, in contrast to depressive symptoms, which are considered to be an affliction or reaction to events, optimism is a relative stable trait and one of the components of personality. Any differences in reported optimism over time appear to be limited and reverberate around what can be called an internal 'thermostat' of optimism.[24] Although the level of optimism after treatment in general did not significantly change in our patients, increase in LOT-R score was significantly higher in those who achieved remission compared to those who did not. Therefore, there may be a small state component to dispositional optimism. Our results also suggest that optimistic patients suffered less from depressive symptoms which in turn were influenced by arthritis related symptoms, especially pain and unwell being. Also optimism influences pain and therefore possibly symptoms of arthritis. In general, baseline optimism has been related to slower disease progression and more efficient adjustment and coping strategies.[18,25,26]

A limitation of our study is that we chose self-report questionnaires to assess depressive symptoms severity and optimism because they are easy to answer and little time consuming. With the use of a structured psychiatric interview the assessment of depressive symptoms in relation to RA disease activity might have been more extensive. The BDI-II provides a numerical score what makes it easy to assess improvement or reduction of the severity of depressive symptoms over time, and a means to classify depressive symptoms severity. In view of the

generally minimal reported depressive symptoms, we believe that the results are of scientific interests rather than of clinical significance.

We looked at optimism as a different focus on mood, and chose the LOT-R to assess whether scores increase or decrease over time or in relation to changes in disease activity. However, although there are numerous reports on baseline optimism in relation to changes in aspects of (coping with) chronic illnesses, the literature on changes in repeated measurements of LOT-R scores in relation to changes in disease activity in patients with a chronic disease are scarce. Previous studies on dispositional optimism in rheumatoid arthritis had cross-sectional designs, which therefore could not analyze effects on optimism in time.[27-29]

In conclusion, among these patients with early RA, treated with methotrexate and a tapered high dose of prednisone, generally already minimal depressive symptoms severity decreased with lower disease activity and was significantly lower in patients who achieved remission than in patients who did not. This appears to be mostly due to the relationship of depression severity with symptoms of arthritis (pain and unwell being) rather than signs of inflammation. Dispositional optimism scores in general stay stable over time, although there appeared to be significantly more improvement in optimism when remission was achieved. Our data suggest that depressive symptoms in RA patients may improve if, by targeted treatment, symptoms of RA are optimally suppressed.

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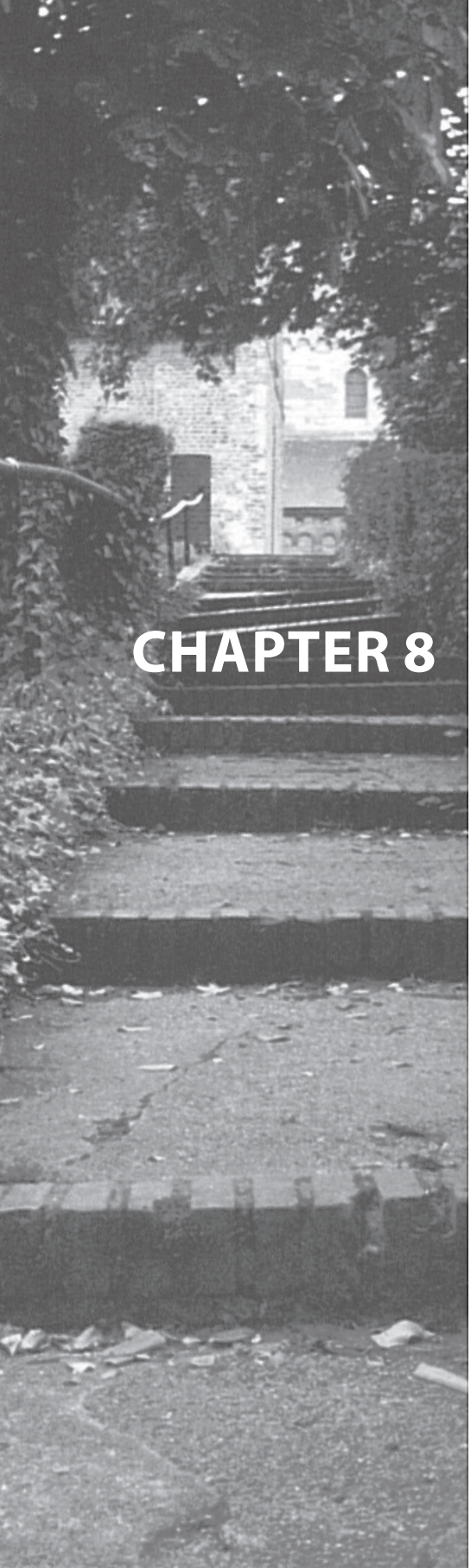

CHAPTER 8

Four-month metacarpal bone mineral density loss predicts radiological joint damage progression after one year in patients with early rheumatoid arthritis - exploratory analyses from the IMPROVED study

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ABSTRACT

Objective

To assess whether metacarpal bone mineral density (BMD) loss after 4 months predicts radiological progression after 1 year of anti-rheumatic treatment in patients with early (rheumatoid) arthritis (RA).

Methods

Metacarpal BMD was measured 4 monthly during the first year by digital X-ray radiogrammetry (DXR-BMD) in patients participating in the IMPROVED study, a clinical trial in 610 patients with recent onset RA (2010 criteria) or undifferentiated arthritis (UA), treated according to a remission (disease activity score<1.6) steered strategy. With Sharp- van der Heijde progression ≥0.5 points after 1 year (yes/no) as dependent variable, univariate and multivariate logistic regression analyses were performed.

Results

Of 428 patients with DXR-BMD results and progression scores available, 28 (7%) had radiological progression after 1 year. Independent predictors for radiological progression were presence of baseline erosions (OR (95%CI) 6.5 (1.7-25)) and early DXR-BMD loss (OR (95%CI) 1.5 (1.1-2.0)). In 366 (86%) patients without baseline erosions early DXR-BMD loss was the only independent predictor of progression (OR (95%CI) 2.0 (1.4-2.9)).

Conclusions

In early (rheumatoid) arthritis patients, metacarpal BMD loss after 4 months of treatment is an independent predictor of radiological progression after 1 year. In patients without baseline erosions, early metacarpal BMD loss is the main predictor of radiological progression.

INTRODUCTION

Early treatment of patients with rheumatoid arthritis (RA) improves disease outcomes including radiological joint damage.[1-3] Identification of patients who will have a more severe disease course may steer early treatment strategies. Since predicting disease outcome is currently not possible in a reliable way for all patients, there is a need for new predictors to improve existing prediction models.[4-7]

Periarticular osteopenia is one of the earliest radiological manifestations in RA and may already be found in the phase of undifferentiated arthritis (UA).[8,9] Metacarpal bone mineral density (BMD) loss may therefore be a potentially new predictor of disease outcome in patients with early (rheumatoid) arthritis. Previous research showed that metacarpal BMD loss is associated with disease activity [10] and metacarpal BMD loss in the first year after diagnosis is predictive for radiological damage up to five years in patients with early RA.[11-13] For clinical practice however, any predictive value of metacarpal BMD loss would be greater if it can be measured earlier in the disease course.

Therefore we investigated whether metacarpal BMD loss after 4 months of treatment, as measured by digital X-ray radiogrammetry (DXR-BMD), may be a predictor of radiological joint damage progression after 1 year in patients with undifferentiated or early RA treated according to a tight control, remission steered treatment strategy.

PATIENTS AND METHODS

Patients and study design

Data from the IMPROVED study were used, a multicenter, randomized clinical trial in 610 patients, including 479 (80%) patients with recent onset RA (according to the 2010 American College of Rheumatology (ACR) / European League Against Rheumatism (EULAR) classification criteria for RA [14] with a symptom duration <2 years), 122 patients with UA (having at least 1 joint clinically assessed as 'arthritis' and 1 other painful joint, clinically suspected of having early RA, regardless of symptom duration) and 9 patients that could not be classified because of missing data. Patients were treated according to a tight control strategy, aimed at achieving remission, defined as a disease activity score (DAS) <1.6 (DAS-remission).[15] All patients started with 4 months of methotrexate (MTX) 25 mg/week and prednisone 60 mg/day tapered to a stable dose of 7.5 mg/day in 7 weeks. Patients in DAS-remission after 4 months started tapering medication, if possible to drug free (early DAS-remission group). Patients not in early DAS-remission were randomized either to MTX 25 mg/week plus hydroxychloroquine (HCQ) 400 mg/day, sulfasalazine (SSZ) 2000 mg/day and prednisone 7.5 mg/day (arm 1) or to MTX 25 mg/week plus adalimumab (ADA) 40 mg/2weeks (arm 2). Some patients who were not in DAS-remission after 4 months, were not randomized and treated outside of protocol

(Outside of Protocol (OP) group). Full details about the IMPROVED study protocol were previously published.[16,17]

In the current analysis we included all patients participating in the IMPROVED study whose radiological progression data after 1 year and at least 1 DXR-BMD result during the first year were available.

Demographic and clinical variables

At baseline the following variables were collected: age, gender, symptom duration, body mass index, current smoking status and alcohol use, calcium intake, postmenopausal status, previous fractures, family history on osteoporosis, anti-citrullinated protein antibodies (ACPA) and rheumatoid factor (RF) status. At baseline and every 4 months, the following clinical and laboratory variables were collected: DAS, including Ritchie Articular Index (RAI), swollen joint count, erythrocyte sedimentation rate (ESR, mm/hr) and visual analogue scale (VAS) for global health, and C-reactive protein (CRP). During the first year, X-rays of hand and feet were made 4 monthly by digital radiography in all patients. Radiological progression, scored using the Sharp/van der Heijde scoring method, was assessed by two independent readers blinded for patient identity and time order of the radiographs.[18] Progression was defined as an increase in Sharp-van der Heijde Score (SHS) of ≥0.5 points. Details on inter-reader reliability were previously published.[17]

Metacarpal BMD measurements

Suitable routine digital X-rays of both hands were used to measure metacarpal BMD using Digital X-ray Radiogrammetry (DXR-BMD) measured by DXR-online (Sectra, Linköping, Sweden), a computerised method that automatically recognises three regions of interest on the second, third and fourth metacarpal bones. At each region, DXR-BMD is estimated from multiple measurements of cortical thickness, bone width and porosity.[19] The mean value of both hands was used in all analyses to avoid bias induced by hand dominance. 'DXR-BMD loss' was defined as a loss in DXR-BMD of ≥1.5 mg/cm^2/4months.[10]

Statistical analysis

Almost half of the available X-rays were found unsuitable for DXR-measurements. This resulted in missing DXR-BMD values in 141/428 patients (33%) at baseline, 73/428 (17%) after 4 months, 148/428 (35%) after 8 months and 140/428 (33%) after 1 year. To avoid possible bias induced by missing data and to increase power, multiple imputation was performed. Ten datasets were created in which missing DXR-values were imputed based on a linear regression model fitting available patient and disease characteristics and DXR-values.[20] Estimates obtained from regression analyses were automatically pooled by SPSS, other multiple estimates were averaged.

Median (IQR) DXR-BMD changes are shown because of a skewed distribution. Mann Whitney U test was used for comparisons of DXR-BMD changes between patients with and without radiological progression. To identify independent predictors of radiological progression, we performed univariate followed by multivariate regression analyses. From previous literature, the following potential predictors for (rapid) radiological progression were identified and entered in a univariate logistic regression model with radiologic progression (yes/no) as dependent variable: presence of ACPA and/or RF, baseline swollen joint count, baseline ESR and CRP levels, baseline total SHS, baseline erosion score and treatment.[4,6,7] In addition, we selected age, gender, fulfilling the 2010 ACR/EULAR criteria for RA and achieving DAS-remission after 4 months. Next to baseline erosion score we also entered presence of erosions, defined as ≥1 erosions, as covariate. Because only 28 (7%) patients had radiological progression, multivariate regression in the total study population was powered for about three variables.[21,22] Therefore, in addition to DXR-BMD loss from baseline to 4 months, we selected the 2 univariate significant predictors (using a significance level of 0.10) with the highest effect size for multiple regression. As radiological progression was present in <10% of the patients and therefore can be classified as 'rare', we argued that Odds Ratios (OR) obtained from all logistic regression analyses can be interpreted as relative risks (RR).[23]

All statistical analyses were conducted with SPSS for Windows version 20.0.

RESULTS

Clinical characteristics

We included 428 patients in the current analyses. Baseline characteristics of these patients did not differ significantly from those participating in the IMPROVED study where no SHS or DXR data were available (data not shown). Twenty-eight (7%) patients had radiological progression after 1 year and 400 (93%) had no radiological progression. For those with radiological progression, the median (IQR) progression score was 0.5 (0.5-1.4). One patient had rapid radiological progression (progression score ≥5 points) [24] after 1 year (18 points).

Compared to patients without progression, patients with progression were older, more often postmenopausal and ACPA positive, and more often fulfilled the 2010 criteria for RA. Furthermore, they had more often ≥1 erosions at baseline and a higher median total baseline SHS and, only at 8 months, a slightly higher DAS. (table 1)

DXR-BMD change

Table 2 shows absolute DXR-BMD values and DXR-BMD changes during the first year. Compared to patients without radiological progression after 1 year, patients with radiological progression had lower absolute DXR-BMD values at baseline and after 4, 8 and 12 months follow up. From baseline to 4 months, median DXR-BMD changes were significantly larger

Table 1: Clinical characteristics at baseline and during one year follow up of the total study group and separate for patients with and without radiological progression.

		Radiologic progression		
	Total population	**Yes**	**No**	**p-value**
Baseline	n=428	n=28	n=400	
Age, years, mean±SD	52 ± 13	58 ± 11	52 ± 13	0.01
Female, no (%)	294 (69)	22 (79)	272 (68)	0.2
BMI, kg/m^2, mean±SD	26 ± 4	25 ± 4	26 ± 4	0.6
Current smoking, no (%)	127 (30)	11 (39)	116 (29)	0.3
Current alcohol use, no (%)	250 (58)	17 (61)	233 (58)	0.9
Postmenopausal status, no (%), n=294	156 (53)	17 (89)	139 (58)	0.01
Previous fractures, no (%)	142 (33)	8 (29)	134 (34)	0.7
Familial osteoporosis, no (%)	72 (17)	6 (21)	66 (17)	0.5
Calcium intake, mg/day, median (IQR)	800 (600-1050)	875 (725-1069)	778 (600-1030)	0.2
25(OH) Vitamine D, nmol/l, median (IQR)	55 (38-75)	46 (25-75)	55 (39-75)	0.3
DAS (mean±SD)	3.2 ± 0.9	3.3 ± 0.9	3.2 ± 0.9	0.8
RA(2010), no (%)	344 (80)	26 (93)	318 (80)	0.04
Symptom duration, weeks, median (IQR)	18 (9-33)	20 (9-47)	18 (9-32)	0.5
ACPA positive, no (%)	247 (58)	23 (82)	224 (56)	0.008
RF positive, no (%)	241 (56)	18 (64)	223 (56)	0.2
ACPA and RF positive, no (%)	205 (48)	19 (68)	186 (47)	0.04
SHS total score	0 (0-0)	0.5 (0-4.5)	0 (0-0)	<0.001
Presence of erosions, no (%)	62 (14)	11 (39)	51 (13)	<0.001
4 months follow up				
DAS (mean±SD)	1.5 ± 0.9	1.5 ± 0.8	1.5 ± 0.9	0.9
Remission, no (%)	275 (64)	17 (61)	258 (65)	0.7
Early remission Group, no (%)	281 (66)	17 (61)	264 (66)	0.6
Arm 1 MTX+SSZ+HCQ+pred, no (%)	60 (14)	4 (14)	56 (14)	0.97
Arm 2 MTX+adalimumab, no (%)	57 (13)	5 (18)	52 (13)	0.5
Outside of Protocol Group, no (%)	30 (7)	2 (7)	28 (7)	0.98
8 months follow up				
DAS (mean±SD)	1.5 ± 0.8	1.8 ± 1.0	1.5 ± 0.8	0.05
Remission, no (%)	246 (57)	12 (43)	234 (61)	0.1
1 year follow up				
Use of Bisphosphonate, no (%)	129 (30)	9 (32)	120 (30)	0.8
Use of Calcium and/ or Vitamine D, no (%)	204 (48)	16 (57)	180 (45)	0.2
DAS (mean±SD)	1.6 ± 0.9	1.6 ± 0.9	1.6 ± 0.9	0.7
Remission, no (%)	235 (55)	16 (57)	219 (55)	0.8
SHS progression	0 (0-0)	0.5 (0.5-1.4)	0 (0-0)	<0.001

ACPA, Anti-Citrullinated Protein Antibodies; arm 1, patients not in early remission who were randomized to arm 1; arm 2, patients not in early remission who were randomized to arm2; BMI, Body Mass Index (kg/m2); DAS, Disease Activity Score; Early remission group, patients who were in remission after 4 months and started tapering medication; HCQ, hydroxychloroquine; IQR, interquartile range; MTX, methotrexate; no, number; Outside of Protocol group, patients not in early remission but not randomized and treated outside the protocol; Presence of erosions, defined as ≥1 erosions; pred, prednisone; RA(2010), rheumatoid arthritis according to the ACR/EULAR 2010 classification criteria for RA; RF, Rheumatoid Factor; remission, defined as DAS<1.6; SD, standard deviation; SHS, Sharp- van der Heijde Score; SSZ, sulfasalazine.

Table 2: Metacarpal bone mineral density measured by digital X-ray radiogrammetry during the first study year of the total study population and separate for patients with and without radiological progression.

	Time point		SHS progression		
	(months)	Total n=428	Yes: n=28	No: n=400	p-value
DXR-BMD g/cm^2, median (IQR)	0	0.593 (0.527-0.640)	0.558 (0.501-0.601)	0.597 (0.529-0.642)	0.03
	4	0.590 (0.526-0.637)	0.546 (0.486-0.587)	0.593 (0.529-0.640)	0.008
	8	0.590 (0.525-0.639)	0.544 (0.482-0.589)	0.593 (0.528-0.642)	0.009
	12	0.585 (0.522-0.636)	0.541 (0.472-0.586)	0.588 (0.524-0.638)	0.008
Change in DXR-BMD mg/cm^2, median (IQR)	0 - 4	-2.4 (-7.6 ; 2.2)	-9.6 (-15.2 ; -2.7)	-2.0 (-7.2 ; 2.5)	0.007
	4 - 8	-1.1 (-6.0 ; 3.2)	-2.2 (-8.1 ; 3.9)	-1.1 (-5.8 ; 3.1)	0.5
	8 -12	-3.1 (-9.0 ; 1.3)	-4.5 (-14.0 ; 0.05)	-3.1 (-8.7 ; 1.5)	0.3
	0 - 12	-5.7 (-15.4 ; 0.6)	-15.8 (-27.4 ; -2.3)	-5.4 (-14.2 ; 0.9)	0.007
Change in DXR-BMD, % from baseline	0 - 4	-0.4 (-1.3 ; 0.4)	-1.7 (-2.9 ; -0.5)	-0.3 (-1.2 ; 0.4)	0.007
	4 - 8	-0.2 (-1.1 ; 0.5)	-0.4 (-1.5 ; 0.7)	-0.2 (-1.0 ; 0.5)	0.5
	8 -12	-0.5 (-1.5 ; 0.2)	-0.8 (-2.7 ; 0.008)	-0.5 (-1.5 ; 0.2)	0.2
	0 - 12	-1.0 (-2.7 ; 0.1)	-2.8 (-4.9 ; -0.4)	-0.9 (-2.4 ; 0.2)	0.006

DXR-BMD, metacarpal bone mineral density measured by digital X-ray radiogrammetry; IQR, inter quartile range; SHS progression, defined as progression after 1 year ≥0.5 points.

in patients with radiological progression (median (IQR) -9.6 (-15.2;-2.7) mg/cm^2) than in patients without (-2.0 (-7.2;2.5) mg/cm^2, p=0.007). Twenty-four (86%) patients with radiological progression had DXR-BMD loss within the first 4 months, compared to 212 (53%) patients without radiological progression (p=0.01). One patient with rapid radiological progression (18 points after 1 year) had a change in DXR-BMD within the first 4 months of -27.4 mg/cm^2.

Treatment steps

Seventeen (61%) patients with radiological progression after 1 year had been in early DAS-remission after 4 months and subsequently had started tapering prednisone to zero, 9 (32%) had not achieved early remission and were randomized, and 2 were treated outside of protocol. Of the 17 in early DAS-remission, 5 patients relapsed after tapering prednisone and restarted it, whereas 12 remained in remission and started tapering MTX to zero. Six patients relapsed after tapering MTX and restarted it and 6 did not relapse and were in drug free remission after 1 year. The median (IQR) early DXR-BMD change of all 17 patients was -10.9 (-14.5;-2.5) mg/cm^2 (corresponding to -2.7 (-3.6;-0.6 mg/cm^2/month)), compared to -1.8 (-7.3;2.4) mg/cm^2 (corresponding to -0.5 (-1.8;0.6 mg/cm^2/month)) in 258 patients who achieved early DAS-remission and had no radiological progression after 1 year (p=0.02). DXR-BMD loss after 4 months was present in 14/17 (82%) patients in early DAS-remission who had radiological progression after 1 year, compared to 134 (52%) patients in early DAS-remission without radiological progression after 1 year (p=0.053).

Table 3a: Univariate logistic regression analysis with radiological progression (yes/no) as dependent variable in the total study population.

	Univariate Logistic regression		
	Crude OR	95%CI	R^2
RA according to 2010 criteria	6.5	0.9-48.8	0.04
Presence of baseline erosions	4.4	2.0-10.0	0.07
ACPA/RF			
Both negative	ref		0.04
One positive	2.6	0.6-11.3	
Both positive	3.9	1.1-13.2	
Early DXR-BMD loss, mg/cm^2/month	1.4	1.1-1.8	0.13
Female gender	1.7	0.7-4.4	0.01
Erosion score at baseline	1.1	0.99-1.1	0.01
Baseline total SHS	1.1	0.996-1.0	0.02
Age, years	1.0	1.0-1.1	0.04
Baseline ESR	1.0	0.999-1.0	0.02
Baseline CRP	1.0	0.997-1.0	0.01
Baseline TJC	0.97	0.9-1.1	0.003
Treatment Group			
Early remission group	ref		0.003
Arm 1 MTX+SSZ+HCQ+pred	1.1	0.4-3.4	
Arm 2 MTX+adalimumab	1.5	0.5-4.2	
Outside of Protocol group	1.1	0.2-5.1	
Early DAS-remission	0.8	0.4-1.9	0.001

ACPA, anti-citrullinated protein antibodies; arm 1, patients not in early remission who were randomized to methotrexate (MTX), sulfasalazine (SSZ), hydroxychloroquine (HCQ) and low dose prednisone; arm 2, patients not in early remission who were randomized to MTX plus adalimumab; CI, confidence interval; CRP, C-reactive protein; DXR-BMD, metacarpal bone mineral density measured by digital X-ray radiogrammetry; Early DXR-BMD loss, change in DXR-BMD between baseline and 4 months; Early remission group, patients who were in remission after 4 months and started tapering medication; Early DAS-remission, remission (DAS<1.6) after 4 months; Erosion score, Sharp-van der Heijde erosion score; ESR, erythrocyte sedimentation rate in mm/hr; OR, odds ratio; Outside of protocol group, patients not in early remission but not randomized and treated outside the protocol; Presence of baseline erosions, defined as ≥1 erosions at baseline; RA, rheumatoid arthritis according to the 2010 ACR/EULAR classification criteria; RF, rheumatoid factor; ref, reference category; SHS, Sharp-van der Heijde Score; TJC, tender joint count.

Table 3b: Multivariate logistic regression with radiologic progression (yes/no) as dependent variable in the total study population.

Multivariate logistic regression	**Adjusted OR**	**95%CI**
Presence of baseline erosions	3.9	1.6-9.5
Early DXR-BMD loss, mg/cm^2/month	1.4	1.1-1.7
RA according to 2010 criteria	4.9	0.6-37

CI, confidence interval; DXR-BMD, metacarpal bone mineral density measured by digital X-ray radiogrammetry; Early DXR-BMD loss, change in DXR-BMD between baseline and 4 months; OR, odds ratio; Presence of baseline erosions, defined as ≥1 erosions, RA, rheumatoid arthritis according to the 2010 ACR/EULAR classification criteria.

Predictors of radiological progression

Univariate predictive variables for radiologic progression after 1 year were: fulfilling the 2010 criteria for RA (p=0.07), presence of baseline erosions (yes/no) (p<0.001), presence of both ACPA and RF (p=0.03), early DXR-BMD loss after 4 months (p=0.008), baseline total SHS score (p=0.07), age (p=0.01), baseline ESR (p=0.06) and baseline tender joint count (p=0.05). Female gender, presence of either ACPA or RF, symptom duration, baseline erosion score, CRP level and treatment group were not predictive. Achieving DAS-remission after 4 months was also not predictive for radiological progression after 1 year.(table 3a)

Together with early DXR-BMD loss, presence of baseline erosions and fulfilling the 2010 criteria for RA were selected for inclusion in the multivariate regression analysis. Both presence of baseline erosions and early DXR-BMD loss were predictive for radiological progression after one year independent of each other and independent of fulfilling the 2010 criteria for RA.(table 3b).

In an additional multivariate model including early DXR-BMD loss, presence of baseline erosions and presence of both ACPA and RF, presence of both ACPA and RF was not an independent predictor of radiological progression, whereas DXR-BMD loss and presence of baseline erosions both were (data not shown).

After leaving out the one patient with rapid radiological progression, the results above did not significantly change (data not shown).

Patients without baseline erosions

In 366 (86%) patients no baseline erosions were present. Of these 366 patients, 17 patients (5%) showed radiological progression after 1 year (61% of all 28 patients with radiological progression) and 349 (95%) did not. Median DXR-BMD change from baseline to 4 months was -11.8 (-16.7;-4.7) mg/cm^2 in patients with progression and -2.0 (-7.0;2.4) mg/cm^2 in patients without progression (corresponding to -2.9 (-4.2;-1.2) and -0.5 (-1.7;0.6) mg/cm^2/months, respectively). Univariate significant predictors for progression after 1 year in patients without baseline erosions were age (p=0.004), baseline total SHS (in these patients reflecting baseline joint space narrowing) (p=0.009), baseline ESR level (p=0.096) and early DXR-BMD loss (p=0.02).(table 4a)

Early DXR-BMD loss and total baseline SHS were selected for inclusion in the multivariate regression analysis. Early DXR-BMD loss was predictive for radiological progression after 1 year independent of baseline total SHS in patients without baseline erosions.(table 4b)

Table 4a: Univariate logistic regression analysis with radiological progression (yes/no) as dependent variable in patients without baseline erosions.

	Univariate Logistic regression		
	Crude OR	95%CI	R^2
RA according to 2010 criteria	4.1	0.5-31.3	0.02
ACPA/RF			
Both negative	ref		0.03
One positive	3.0	0.5-17	
Both positive	3.2	0.7-15	
Early DXR-BMD loss, mg/cm^2/month	1.4	1.1-1.9	0.13
Female gender	2.1	0.6-7.5	0.01
Baseline total SHS	1.3	1.1-1.6	0.06
Age, years	1.1	1.0-1.1	0.08
Baseline ESR, mm/hr	1.0	0.997-1.0	0.02
Baseline CRP	1.0	0.99-1.0	0.002
Baseline TJC	0.97	0.9-1.1	0.004
Treatment Group			
Early remission group	ref		0.01
Arm 1 MTX+SSZ+HCQ+pred	1.6	0.4-5.9	
Arm 2 MTX+adalimumab	1.7	0.5-6.6	
Outside of Protocol group	1.8	0.4-8.8	
Early DAS-remission	0.6	0.2-1.7	0.007

ACPA, anti-citrullinated protein antibodies; arm 1, patients not in early remission who were randomized to methotrexate (MTX), sulfasalazine (SSZ), hydroxychloroquine (HCQ) and low dose prednisone; arm 2, patients not in early remission who were randomized to MTX plus adalimumab; CI, confidence interval; CRP, C-reactive protein; DXR-BMD, metacarpal bone mineral density measured by digital X-ray radiogrammetry; Early DXR-BMD loss, change in DXR-BMD between baseline and 4 months; Early remission group, patients who were in remission after 4 months and started tapering medication; Early DAS-remission, remission (DAS<1.6) after 4 months; ESR, erythrocyte sedimentation rate in mm/hr; OR, odds ratio; Outside of protocol group, patients not in early remission but not randomized and treated outside the protocol; RA, rheumatoid arthritis according to the 2010 ACR/EULAR classification criteria; RF, rheumatoid factor; ref, reference category; SHS, Sharp-van der Heijde Score; TJC, tender joint count.

Table 4b: Multivariate logistic regression with radiologic progression (yes/no) as dependent variable in patients without baseline erosions

Multivariate logistic regression	Adjusted OR	95%CI
Early DXR-BMD loss, mg/cm^2/month	1.4	1.1-1.8
Baseline total SHS	1.3	1.0-1.6

CI, confidence interval; DXR-BMD, metacarpal bone mineral density measured by digital X-ray radiogrammetry; Early DXR-BMD loss, change in DXR-BMD between baseline and 4 months; OR, odds ratio; SHS, Sharp-van der Heijde Score.

DISCUSSION

In patients with early rheumatoid or undifferentiated arthritis, metacarpal BMD loss measured by DXR after four months of treatment with MTX and a tapered high dose of prednisone is predictive for future joint damage after 1 year of remission steered treatment. In patients without baseline erosions (86%), metacarpal BMD loss was the main predictor of future joint damage.

These data suggest that DXR measurements over a period of 4 months from baseline can help to decide which patients with early arthritis should start anti-rheumatic treatment to prevent joint damage or damage progression, one of the main goals in the treatment of RA.[25] Early treatment and suppression of disease activity has been shown to be associated with better suppression of radiological damage progression.[1-3] To facilitate this, in 2010 new classification criteria for RA were formulated.[14] In the IMPROVED trial we included not only patients with RA (according to the 2010 classification criteria) but also patients with UA, who were judged to represent RA in an early phase of the disease by the treating rheumatologist. Starting treatment so early in disease course carries the risk of overtreatment of patients who are misdiagnosed as RA, but a treatment delay means risking irreversible joint damage progression.

To individualize treatment, predictive factors for damage progression have been identified and prediction models built.[4,6,7] But in particular in patients without baseline damage, predicting which patients will develop joint damage may be difficult. We predicted metacarpal BMD loss since this was linked with both disease activity and joint damage progression in patients with early and established RA, and metacarpal BMD loss after 1 year has been shown to have predictive value additional to known predictors.[11,12] Our paper is the first to report metacarpal BMD changes already after 4 months, and we found that changes do occur.

Ideally, an outcome predictor can be identified already at baseline. In this early arthritis population, presence of baseline erosions was the only independent baseline predictor of radiological progression after 1 year besides metacarpal BMD loss after 4 months. Another obvious outcome after 4 months, remission yes or no, was not predictive of radiological progression after 1 year. Some patients who had radiological joint damage after 1 year even were in remission throughout the whole year and tapered all medication according to the study protocol. Our results indicate that after 4 months, a strong predictor of progression may help to decide if adjustments of the chosen treatment strategy should be made in patients with early arthritis.

One limitation of this study is the fact that, due to the inclusion of patients with early and relatively mild disease, progressively treated with the aim of achieving remission, only a few patients had radiological damage progression. Our results however reached statistical significance, although we acknowledge that the damage scores are hardly of clinical relevance this early in the disease phase. But as RA treatment more and more aims at achieving total

disease and damage control in an early phase of the disease, we think that our findings may be relevant for daily practice.

Another limitation was that we found many of the 'routinely' acquired radiographs to be unsuitable for DXR. To handle missing metacarpal BMD data, we performed multiple imputation [20] to account for potential bias caused by data 'missing at random', meaning that missingness depends on other observed patient characteristics rather than on the fact whether metacarpal BMD measurements were possible or not.

A third possible limitation may be that, as DXR-measurements in this study were done in retrospect on X-rays taken in 12 different hospitals using imaging protocols not adjusted to DXR, precision of the method may be lower than previously published. DXR-BMD has been shown to have a very high short and long term precision in both in vitro cadaver studies (coefficients of variation (CV) of 0.22 to 1%) and in one cohort study and one clinical trial (CV of 0.25 to 0.46%).[26-29] However, supported by the consistency of our results, precision in this study may still be considered as high.

If metacarpal BMD is to be applied in clinical practice using the DXR online method, neither low precision nor missing values may be problematic, as X-rays will then be taken according to a predefined protocol (Sectra, Sweden). Precision may reach values described above, and in case of mal positioning, direct feedback will be given, which makes it more suitable for use in clinical practice.

In conclusion, we showed that loss of metacarpal bone mineral density measured by DXR after the first 4 months of treatment is an independent predictor of future bone damage in patients with early (rheumatoid) arthritis. This suggests that 4 monthly metacarpal BMD measurements can help to guide treatment decisions in individual patients or may be added to improve the predictive value of existing prediction models for disease outcome in RA.

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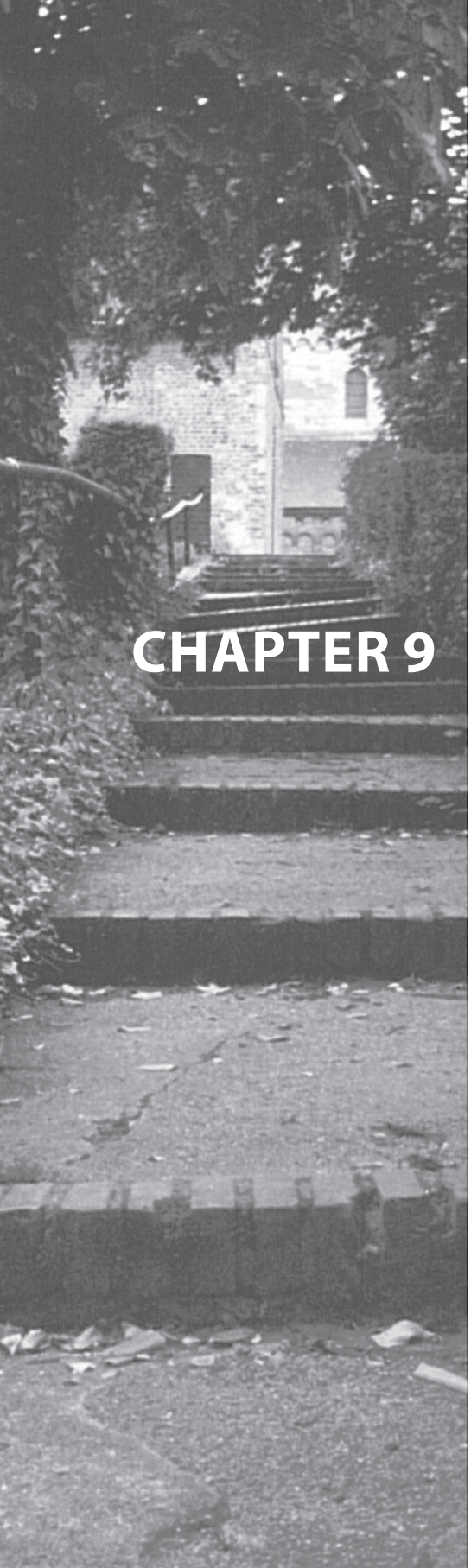

CHAPTER 9

Changes in metacarpal bone mineral density in patients with undifferentiated and early rheumatoid arthritis during one year of remission steered treatment

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Submitted

ABSTRACT

Objective

To investigate possible determinants of localized bone loss in patients with early arthritis.

Methods

Of 610 patients with early arthritis in the IMPROVED study, 442 had ≥1 measurements of metacarpal bone mineral density (BMD) by Digital X-ray Radiogrammetry (DXR-BMD) during year 1 of remission (Disease Activity Score <1.6) steered treatment. Initial treatment consisted of methotrexate and a tapered high dose of prednisone. If remission was achieved medication was tapered, if not, patients were randomized to combination therapy including low dose prednisone or adalimumab. DXR-BMD loss (≥1.5 mg/cm^2/4 months, ≥4.6 mg/cm^2/year) or gain (≥4.6 mg/cm^2/year) was compared between treatment and patient groups. Predictors for DXR-BMD loss were assessed.

Results

DXR-BMD loss occurred in 246 (56%) and 243 (55%) patients after 4 months and 1 year, DXR-BMD gain in 60 (14%) patients after 1 year. Of patients with DXR-BMD loss after 4 months, 32 (13%) regained the total loss within 1 year. Age and postmenopausal status were independent predictors of DXR-BMD loss after 1 year. Randomized patients less often showed DXR-BMD loss after 1 year than patients who achieved early remission (52 (44%) versus 170 (59%), p=0.02). Based on small numbers, patients treated with adalimumab showed the smallest loss and most often gain (14 (54%)).

Conclusions

After 1 year of remission steered treatment, metacarpal BMD loss occurs in more than half of patients with early arthritis. Our data may suggest that although initial combination therapy including a tapered high dose of prednisone may induce remission in a large proportion of patients, it may have at least a temporary negative effect on localized BMD.

INTRODUCTION

Bone loss is a clinical feature in patients with rheumatoid arthritis (RA) and occurs generalized as well as localized around inflamed joints.[1] Generalized bone loss may be caused by prolonged disease activity, immobility by functional impairment and anti-rheumatic medication such as corticosteroids.[2-5] Earlier in the disease course of RA localized bone loss occurs, possibly due to localized inflammatory processes.[1,6] In an earlier study we have shown that in RA patients who were in clinical remission for at least 1 year, an increase in localized bone mineral density (BMD) can occur. This was not found in patients who had high or even low disease activity.[7] Measuring localized bone loss in patients with early (rheumatoid) arthritis in association with treatment and treatment response may be helpful to understand possible determinants of bone loss in rheumatoid arthritis. To investigate this, we performed four-monthly metacarpal BMD measurements by Digital-X-ray Radiogrammetry (DXR, Sectra, Linköping, Sweden) during the first year in patients participating in the IMPROVED study, a remission steered clinical trial in 610 patients with undifferentiated arthritis (UA) or early RA.[8,9]

METHODS

Patients and study design

IMPROVED is a multicentre, randomized clinical trial in 479 (79%) patients with recent onset RA (according to the 2010 classification criteria for RA [10] with a symptom duration <2 years) and 122 (20%) UA patients (having at least one arthritic and one other painful joint and clinically suspected to represent early RA, regardless of symptom duration). Patients were treated according to a tight control strategy, aimed at achieving remission, defined as a Disease Activity Score (DAS) <1.6.[11] All patients started with 4 months of methotrexate (MTX) 25 mg/week and prednisone 60 mg/day, tapered to a stable dose of 7.5 mg/day in 7 weeks. Patients in remission after 4 months (early remission) started tapering medication, if possible to drug free. Patients who did not achieve early remission were randomized either to MTX 25 mg/week plus hydroxychloroquine (HCQ) 400 mg/day, sulphasalazine (SSZ) 2000 mg/day and prednisone 7.5 mg/day (arm 1) or to MTX 25 mg/week plus adalimumab 40 mg/2weeks (arm 2). Thirty-one patients who did not achieve early remission were not randomized and treated outside of protocol. Full details on the IMPROVED study protocol were previously published.[9]

Demographic and clinical variables

At baseline and every 4 months, the following clinical and laboratory variables were collected: DAS, including Ritchie Articular Index (RAI), swollen joint count, erythrocyte sedimentation rate (ESR, mm/hr) and visual analogue scale (VAS, mm) for global health,[12] and C-reactive

protein (CRP). Use of calcium and/or vitamin D supplements and bisphosphonates was assessed after one year.

Metacarpal BMD measurements

At baseline, 4 months, 8 months and 1 year, digital plain radiographs of hands and feet were made according to the protocol of the local hospitals' radiology departments. No moulds or positioning devices were used, no specific technical adaptions were applied. Metacarpal BMD was measured on X-rays of both hands using Digital X-ray Radiogrammetry (DXR-BMD) by dxr-online (Sectra, Linköping, Sweden). Three regions of interest are automatically recognized on the second, third and fourth metacarpal bone. At each region, DXR-BMD is estimated from multiple measurements of cortical thickness, bone width and porosity.[13] The mean value of both hands was used in all analyses to maximize precision and avoid bias induced by hand dominance. Previously, DXR-BMD measurements have been shown to have a very high short and long term precision in both in vitro cadaver studies (coefficients of variation (CV) of 0.22 to 1%) and in one cohort study and one clinical trial (CV of 0.25 to 0.46%).[14-17] However, because measurements in this study were done in retrospect, precision may be lower than previously published.

Absolute values of DXR-BMD were expressed in g/cm^2, changes in DXR-BMD in mg/cm^2/4months or mg/cm^2/year. 'DXR-BMD loss' was defined as a decrease in DXR-BMD ≥1.5 mg/cm^2/4months or ≥4.6 mg/cm^2/year and 'BMD-DXR gain' as an increase in DXR-BMD ≥1.5 mg/cm^2/4months or ≥4.6 mg/cm^2/year.[7]

Of the 610 patients included, 442 patients had least one DXR-BMD measurement during the first year. Of the other patients, four-monthly radiographs were available but found unsuitable for DXR-measurements by Sectra,[18] as were baseline radiographs in 148 patients (33%), 4 months-radiographs in 78 patients (18%), 8 months-radiographs in 155 patients (35%) and 1 year radiographs in 148 patients (33%) of the 442 patients included in the current analysis.

Statistical analysis

Median (IQR) DXR-BMD (change) values were shown because of skewed distributions. Because of missing DXR-BMD values multiple imputation was performed.[19] Ten datasets were created in which missing DXR-values were imputed based on a linear regression model fitting available patient and disease characteristics and DXR-values. Estimates obtained from regression analyses were automatically pooled by SPSS, other multiple estimates were averaged.

All DXR-BMD changes and percentages loss and gain were obtained from the imputed dataset. Because of the small number of patients, separate values for arm 1 and 2 were obtained from the original dataset. Non-parametric test were used for comparisons of DXR-BMD changes between various patient groups. Absolute DXR-BMD levels over time were compared between various patient groups by linear mixed models, performed on the original dataset, with time (study visit) and fulfilling of the 2010 classification criteria for RA (yes/no) or having

achieved early remission (yes/no) or being in continuous remission throughout the first study year (yes/no) as fixed effects, in an unstructured covariance structure. Regression analyses were performed on the imputed dataset with DXR-BMD loss (yes/no) as binomial dependent variable. Statistical analyses were conducted with SPSS for Windows version 20.0.

RESULTS

Baseline and follow up clinical characteristics

Of the 442 patients selected for the current analysis, 355 (80%) patients fulfilled the 2010 criteria for RA at baseline, 82 (19%) did not (UA) and 5 patients had missing data. Compared to RA patients, UA patients had a lower disease activity (mean DAS (SD) 2.7 (0.7) versus 3.3 (0.9), p<0.001), were less often female (47/82 (57%) versus 247/355 (70%), p=0.2) and female patients less often were in a postmenopausal state (21/82 (41%) versus 134/355 (54%), p=0.03). Furthermore, 3 UA patients were anti-citrullinated protein antibodies (ACPA) positive and 3 rheumatoid factor (RF) positive, compared to respectively 246 (69%) and 244 (69%) of the RA patients (p<0.001). After 4 months, early remission was achieved in 55 UA patients (67%) and 226 RA patients (64%) (p=0.6).(table 1)

Changes in DXR-BMD

From baseline to 4 months, median (IQR) DXR-BMD loss in all patients was -2.6 (-8.1;2.2) mg/cm^2 (with a maximum of -40.3 mg/cm^2 and a minimum of 44.0 mg/cm^2), -1.5 (-7.3;3.7) mg/cm^2 in UA patients and -2.8 (-8.6;2.1) mg/cm^2 in RA patients (p=0.2). DXR-BMD loss, defined a decrease ≥1.5 mg/cm^2, was present in 246 (56%) patients, 41 (50%) UA and 205 (58%) RA patients (p=0.3). DXR-BMD gain, defined as an increase ≥1.5 mg/cm^2, was present in 129 (29%) patients, 27 (33%) UA and 102 (29%) RA patients (p=0.5).

From baseline to 1 year, median (IQR) DXR-BMD loss in all patients was -6.4 (-16.1;0.6) mg/cm^2 (with a maximum of -80.0 mg/cm^2 and a minimum of 39.8 mg/cm^2), -4.1 (-13.1;2.9) mg/cm^2 in UA patients and -6.9 (-16.6;0.1) mg/cm^2 in RA patients (p=0.08). (table 2) DXR-BMD loss after 1 year, defined as a decrease ≥4.6 mg/cm^2, was present in 243 (55%) patients, 40 (49%) UA patients and 203 (57%) RA patients (p=0.2). DXR-BMD gain after 1 year, defined as an increase ≥4.6 mg/cm^2, was present in 60 (14%) patients, 15 (18%) UA patients and 45 (13%) RA patients (p=0.3).

To investigate whether DXR-BMD loss from baseline to 4 months was regained in the following months, we evaluated changes in DXR-BMD from 4-12 months in the 246 patients with DXR-BMD loss from baseline to 4 months. In these patients, the additional median (IQR) DXR-BMD loss from 4-12 months was -3.1 (-12.0;2.5) mg/cm^2. In 123 (50%) patients the additional DXR-BMD loss was ≥3.1 mg/cm^2/8months, 56 (23%) patients had DXR-BMD gain ≥3.1 mg/cm2/8months and 67 (27%) patients had a stable DXR-BMD (loss or gain <3.1 mg/

Table 1: Demographic, clinical and laboratory characteristics at baseline and follow up of the total study population and separate for patients with undifferentiated arthritis and rheumatoid arthritis (according to the 2010 classification criteria).

	Total population n=442	UA n=82	RA n=355*	p-value
Baseline				
Age, years, mean±SD	52 ± 14	52 ± 15	52 ± 13	0.8
Female, no (%)	303 (69)	47 (57)	247 (70)	0.2
BMI, kg/m^2, mean±SD	26 ± 4	26 ± 4	26 ± 5	0.98
Current smoking, no (%)	132 (30)	18 (22)	112 (32)	0.1
Current alcohol use, no (%)	259 (59)	47 (57)	209 (59)	0.8
Postmenopausal status, no (%), n=268 women**	159 (59)	21 (41)	134 (54)	0.03
Calcium intake, mg/day, median (IQR)	800 (600-1050)	825 (725-1075)	800 (600-1050)	0.2
25(OH) Vitamine D, nmol/l, median (IQR)	55 (37-75)	52 (39-74)	56 (37-76)	0.7
DAS (mean±SD)	3.2 ± 0.9	2.7 ± 0.7	3.3 ± 0.9	<0.001
Symptom duration, weeks, median (IQR)	18 (9-33)	17 (8-28)	18 (9-34)	0.2
ACPA positive, no (%)	253 (57)	3 (4)	246 (70)	<0.001
RF positive, no (%)	251 (57)	3 (4)	244 (71)	<0.001
SHS total score, median (IQR)	0 (0-0)	0 (0-0)	0 (0-0)	0.9
Presence of erosions, no (%)	62 (14)	7 (9)	54 (15)	0.1
Follow up				
Remission after 4 months, no (%)	284 (64)	55 (67)	226 (64)	0.6
Remission after 1 year, no (%)	240 (54)	48 (59)	189 (53)	0.3
Calcium and/or vitamin D suppletion during year 1, no (%)	210 (48)	36 (44)	172 (48)	0.5
Bisphosphonate use year 1, no (%)	135 (31)	28 (34)	106 (30)	0.5
Treatment groups				
Early remission group, no (%)	289 (65)	57 (70)	229 (65)	
Arm 1: MTX+SSZ+HCQ+prednisone, no (%)	60 (14)	13 (16)	47 (13)	
Arm 2: MTX+adalimumab, no (%)	57 (13)	7 (9)	48 (14)	
Outside of protocol group, no (%)	31 (7)	4 (5)	27 (8)	

*Five patients could not be classified according to the 2010 classification criteria for RA because of missing data. **35 women had missing data on postmenopausal status.
ACPA, anti-citrullinated protein antibodies; BMI, body mass index; DAS, disease activity score; IQR, inter quartile range; no, number; RA, rheumatoid arthritis (2010 ACR/EULAR classification criteria); RF, rheumatoid factor; SD, standard deviation; SHS, Sharp-van der Heijde Score; UA, undifferentiated arthritis.

cm^2/8months). Only 32 (13%) patients regained all the DXR-BMD loss (or more) that occurred from baseline to 4 months.

Table 3 shows results of the univariate regression analyses with DXR-BMD loss after 4 months and 1 year as dependent outcomes. Of tested baseline variables, age and postmenopausal status were predictors for DXR-BMD loss after 4 months (respectively OR (95%CI) 1.03 (1.01-1.05), p=0.002 and 2.9 (1.6-5.2), p=0.001), although not independently of each other. DAS at 4 months was not associated with DXR-BMD loss after 4 months (0.96 (0.7-1.3), nor

Table 2: Metacarpal bone mineral density measured by digital X-ray radiogrammetry during the first year for all patients and separate for patients with undifferentiated and rheumatoid arthritis.

	Time point (months)	Total n=442	UA patients n=82	RA patients n=355	p-value
Absolute DXR-BMD g/cm^2, median (IQR)	0	0.592 (0.528-0.640)	0.599 (0.538-0.647)	0.590 (0.527-0.638)	0.6
	4	0.590 (0.528-0.637)	0.602 (0.535-0.653)	0.589 (0.527-0.634)	0.4
	8	0.590 (0.585-0.639)	0.598 (0.537-0.645)	0.589 (0.525-0.636)	0.5
	12	0.585 (0.523-0.637)	0.589 (0.525-0.649)	0.585 (0.522-0.635)	0.4
Change in DXR-BMD mg/cm^2, median (IQR)	0 - 4	-2.6 (-8.1 ; 2.2)	-1.5 (-7.3 ; 3.7)	-2.8 (-8.6 ; 2.1)	0.2
	4 - 8	-1.4 (-6.5 ; 3.3)	-1.5 (-6.5 ; 3.0)	-1.4 (-6.6 ; 3.4)	0.6
	8 -12	-2.9 (-8.9 ; 1.8)	-1.4 (-7.8 ; 3.1)	-3.5 (-9.1 ; 1.6)	0.2
	0 - 12	-6.4 (-16.1 ; 0.6)	-4.1 (-13.1 ; 2.9)	-6.9 (-16.6 ; 0.1)	0.08
DXR-BMD loss ≥4.6 mg/cm^2 after 1 year, no (%)		243 (55)	40 (49)	203 (57)	0.2
DXR-BMD gain ≥4.6 mg/cm^2 after 1 year, no (%)		60 (14)	15 (18)	45 (13)	0.3

DXR-BMD, bone mineral density measured by digital X-ray radiogrammetry; IQR, interquartile range; no, number; RA, rheumatoid arthritis according to the 2010 ACR/EULAR classification criteria; UA, undifferentiated arthritis.

Table 3: Univariate regression analyses with metacarpal bone mineral density loss after 4 months and 1 year (yes/no) measured by digital X-ray radiogrammetry as dependent variable.

	4 months DXR-BMD loss		1 year DXR-BMD loss	
Univariate regression analyses	Crude OR	95% CI	Crude OR	95% CI
Age	1.03	1.01-1.05	1.07	1.04-1.09
Female gender	0.9	0.6-1.4	1.09	0.7-1.8
Postmenopausal status	2.9	1.6-5.2	7.2	3.5-14.8
Baseline DAS	1.03	0.8-1.3	1.03	0.8-1.4
Baseline DXR-BMD (g/cm^2)	0.7	0.02-24.2	0.02	0.001-0.4
Presence of ACPA	1.5	0.9-2.6	1.3	0.9-2.0
Presence of RF	1.0	0.6-1.8	1.02	0.6-1.7
Fulfilling 2010 criteria for RA	1.3	0.7-2.4	1.4	0.8-2.3
Symptom duration	1.003	0.99-1.01	0.996	0.985-1.006
Baseline TJC	0.97	0.93-1.02	0.97	0.92-1.01
Baseline SJC	1.02	0.98-1.1	1.009	0.96-1.06
Baseline ESR	1.01	0.995-1.02	1.01	1.001-1.02
Baseline CRP	1.0	0.99-1.02	1.01	1.001-1.02
Baseline SHS	1.1	0.98-1.2	1.2	1.006-1.3
Baseline erosions (yes/no)	0.7	0.4-1.3	0.8	0.4-1.5

ACPA, anti-citrullinated protein antibodies; CRP, C-reactive protein; DAS, disease activity score; DXR-BMD, bone mineral density measured by digital X-ray radiogrammetry, ESR, erythrocyte sedimentation rate; RA, rheumatoid arthritis; RF, rheumatoid factor; SHS, Sharp-van der Heijde Score; SJC, swollen joint count; TJC, tender joint count.

was achieving remission after 4 months (0.96 (0.6-1.5)). Univariate predictors for DXR-BMD loss after 1 year were age (1.07 (1.04-1.09), p<0.001), postmenopausal status (7.2 (3.5-14.8, p<0.001), baseline DXR-BMD (0.02 (0.001-0.4), p=0.012), both baseline ESR (1.01 (1.001-1.02), p=0.03) and CRP (1.01 (1.001-1.02), p=0.03) and baseline Sharp-van der Heijde Score (SHS) (1.2 (1.006-1.3), p=0.04). Of these, again only age and postmenopausal status were independent predictors of DXR-BMD loss after 1 year (respectively 1.04 (1.003-1.07), p=0.03 and 3.3 (1.4-7.9), p=0.008). Regression analyses performed on the original dataset showed similar trends (data not shown).

Early remission versus randomization

To evaluate how early remission and subsequent tapering of prednisone affects DXR-BMD, we compared the results of the 289 (65%) patients who achieved early remission (of whom 277 tapered and stopped prednisone) with the 117 (26%) patients who did not achieve early remission and were randomized to either MTX, SSZ, HCQ and low dose prednisone (arm 1, 60 patients) or MTX plus adalimumab (arm 2, 57 patients).

At baseline, patients who achieved early remission had a lower baseline disease activity than randomized patients and after 1 year they more often achieved remission than randomized patients. Also, fewer patients in early remission were female. On the other hand, more patients in early remission were ACPA and RF positive and they less often used bisphosphonates than randomized patients.(table 4) Overall during the first year, absolute DXR-BMD levels were higher in patients who had achieved early remission than in patients who were randomized, although the difference was not significant (mean difference 10.3 (-6.4;26.9), p=0.2, randomized patients set as reference).

After 1 year, patients in early remission had a larger median (IQR) DXR-BMD loss than randomized patients (-7.2 (-16.3;-0.1) versus -3.4 (-13.3;2.4), p=0.051).(table 5) DXR-BMD loss ≥4.6 mg/cm^2 after 1 year occurred in 170 (59%) patients who had been in early remission and in 52 (44%) patients who were randomized (p=0.02). DXR-BMD gain ≥4.6 mg/cm^2 after 1 year was present in 36 (12%) patients who achieved early remission and 22 (19%) patients who were randomized (p=0.2). In the original data set, DXR-BMD gain ≥4.6 mg/cm^2/year was present in 7/33 (21%) patients in arm 1 and 14/26 (54%) in arm 2 (p=0.015).

The smallest DXR-BMD loss during the first year was seen between 4-8 months, both in patients who achieved early remission and in randomized patients (median (IQR) -2.0 (-7.1;3.0) and -0.3 (-5.0;4.3) mg/cm^2 respectively, p=0.07). (table 5) In the original data set, the median (IQR) DXR-BMD change from 4-8 months in arm 1 (MTX+SSZ+HCQ+low dose prednisone) was -0.8 (-4.6;1.3) mg/cm^2 and in arm 2 (MTX+adalimumab) 2.0 (-3.1;3.6) mg/cm^2 (p=0.16).

Continuous remission versus no continuous remission

Over year 1, 132 (30%) patients were in continuous remission, 285 (64%) were not (in 25 patients remission data were missing on ≥1 time points). Patients in continuous remission

Table 4: Demographic and clinical characteristics and treatment steps at 8 months of patients in remission after 4 months versus randomized patients.

	Early remission n=289	Randomized n=117	p-value
Baseline			
Age, years, mean±SD	52±14	51±14	0.3
Female, no (%)	181 (63)	92 (79)	0.002
Postmenopausal status, no (%), n=241 women**	92 (58)	47 (57)	0.9
DAS, mean±SD	3.1±0.9	3.5±0.9	<0.001
Symptom duration, weeks, median (IQR)	18 (9-32)	19 (8-34)	0.97
ACPA positive, no (%)	179 (62)	57 (49)	0.008
RF positive, no (%)	173 (60)	58 (50)	0.08
SHS total score, median (IQR)	0 (0-0.25)	0 (0-0)	0.6
Presence of erosions, no (%)	44 (15)	18 (15)	0.96
Baseline DXR-BMD g/cm^2, median (IQR)	0.603 (0.532-0.650)	0.582 (0.540-0.627)	0.2
Treatment steps at 8 months follow up			
Restarting prednisone (7.5 mg/day)	62 (21)	-	
Tapering MTX	158 (55)	-	
Tapering SSZ, HCQ and prednisone (arm 1, n=60)	-	20 (33)	
Switching to adalimumab (arm 1, n=60)	-	25 (42)	
Tapering adalimumab (arm 2, n=57)	-	16 (28)	
Increasing adalimumab dose (arm 2, n=57)	-	24 (42)	
No or other steps	69 (24)	32 (27)	
1 year follow up			
Remission, no (%)	194 (67)	36 (31)	<0.001

ACPA, anti-citrullinated protein antibodies; arm 1, randomized to treatment with MTX+SSZ+HCQ+prednisone; arm 2: randomized to treatment with MTX+adalimumab; DAS, disease activity score; DXR-BMD, bone mineral density measured by digital X-ray radiogrammetry; HCQ, hydroxychloroquine; IQR, inter quartile range; mg, milligram; MTX, methotrexate; no, number; RF, rheumatoid factor; SHS, Sharp-van der Heijde Score; SSZ, sulfasalazine; SD, standard deviation.

had a lower baseline disease activity (DAS 2.9 (0.8) versus 3.4 (0.9), p<0.001) and included fewer females (74 (56%) versus 212 (74%), p<0.001), compared to patients not in continuous remission. On the other hand, patients in continuous remission used less often calcium and vitamin D supplements (53 (40%) versus 150 (53%), p=0.007) and bisphosphonates (29 (22%) versus 104 (36%), p=0.003) during the first year. Median baseline DXR-BMD levels of patients in continuous remission were 0.603 (0.546-0.659) mg/cm2 and of patients not in continuous remission 0.589 (0.521-0.637) mg/cm2 (p=0.09). Over the first year, absolute DXR-BMD levels were higher in patients in continuous remission than in patients not in continuous remission, although not significantly (mean difference 12.0 (28.3;4.4) mg/cm2, patients not in continuous remission set as reference, (p=0.15)).

Table 5: Changes in metacarpal bone mineral density measured by digital X-ray radiogrammetry during the first year, separate for patients who achieved early remission and patients who were randomized.

	Time point (months)	Early remission N=289	Randomized N=117	p-value
Change in DXR-BMD mg/cm^2, median (IQR)	0 - 4	-2.7 (-8.4;2.2)	-2.2 (-7.2;2.7)	0.4
	4 - 8	-2.0 (-7.1;3.0)	-0.3 (-5.0;4.3)	0.07
	8 -12	-3.2 (-8.6;1.8)	-2.2 (-8.7;2.7)	0.4
	0 - 12	-7.2 (-16.3;-0.1)	-3.4 (-13.3;2.4)	0.051
DXR-BMD loss ≥4.6 mg/cm2 after 1 year, no (%)		170 (59)	52 (44)	0.02
DXR-BMD gain ≥4.6 mg/cm2 after 1 year, no (%)		36 (12)	22 (19)	0.2

DXR-BMD, bone mineral density measured by digital X-ray radiogrammetry; Early remission, remission after 4 months of treatment with MTX and a tapered high dose of prednisone; IQR, inter quartile range; no, number; randomized, patients who did not achieve early remission and were randomized to either MTX, sulphasalazine, hydroxychloroquine and low dose prednisone or MTX plus adalimumab.

Median (IQR) DXR-BMD loss and percentages patients with DXR-BMD loss ≥4.6 mg/cm^2/year after 1 year were comparable between patients in continuous remission and patients who were not (-6.3 (-14.8;0.1) compared to -6.4 (-16.6;0.6) mg/cm^2, p=0.5 and 72 (55%) versus 157 (55%), p=0.5). DXR-BMD gain was present in 16 (12%) patients who were in continuous remission and in 40 (14%) patients who were not in continuous remission.

DISCUSSION

We investigated metacarpal BMD loss in patients with early (rheumatoid) arthritis, treated initially with MTX and a tapered high dose of prednisone, with subsequent treatment adjustments aiming at remission. This is the first clinical trial in which metacarpal BMD was monitored this intensively and this early in the disease course of RA, while disease activity was effectively suppressed in the majority of patients by the current treatment strategy. However, we are aware that results were obtained from frequent measurements and imputed data and that observed differences generally were small. Future studies are needed to demonstrate the relevance of our results.

Our data suggest that the annual decrease in metacarpal BMD in patients with early arthritis may be somewhat lower than previously found in patients with early RA (varying from 9 to 22 mg/cm^2/year).[15,20-22] However, still more than half of the early arthritis patients had metacarpal BMD loss after 4 months of treatment with MTX and a tapered high dose of prednisone. In subsequent months, only 13% of the patients regained this DXR-BMD loss. Patients who had achieved early remission and tapered medication, showed more metacarpal BMD loss than patients who were randomized to extended combination therapy either including low dose prednisone or adalimumab. Although based on small numbers, we observed that

patients treated with adalimumab showed the smallest loss in metacarpal BMD and most often showed gain after 1 year (54%, compared to 21% in patients randomized to combination therapy including prednisone and 12% of early remission patients).

Our finding that metacarpal BMD loss after 4 months may be present in more than half of the patients with early arthritis, may be due to initial disease activity, the use of prednisone or both. The effect of the initial treatment cannot be elucidated since in the first 4 months all patients receive the same medication. However, results from the regression analyses may suggest that metacarpal BMD loss after 4 months was not dependent of baseline or 4 months disease activity, but only on age and postmenopausal status. This may indicate that the use of a tapered high dose of prednisone initially causes metacarpal BMD loss, a loss that was regained during the subsequent months in only a minority of the patients. Longer follow up data are needed to see whether more patients may regain the loss in the second year or later.

The finding that patients not achieving remission after 4 months who were randomized, may have less metacarpal BMD loss after 1 year and more gain than patients who did achieve early remission, may be explained by the intensive combination treatment that randomized patients received, either including low dose prednisone or adalimumab. Previously, treatment with anti-TNF-alpha or low dose prednisone has been shown to reduce hand BMD loss in patients with early RA.[15,23,24] However, the possibly larger metacarpal BMD loss in the early remission group might also be explained by the finding that randomized patients more often used bisphosphonates.

Despite small patients numbers, our results may suggest that patients treated with combination therapy including adalimumab had even less hand BMD loss and more gain than patients treated with a combination of DMARDs with low dose prednisone. Previously, TNF blockers have been shown to reduce joint damage progression,[25] and generalized as well as hand bone mineral density loss.[23,26-28] It has been suggested that this reduction may occur independently of the clinical response to TNF blockers.[28,29]

We found no differences in metacarpal BMD loss or gain between patients who were in continuous remission during the first year and patients who were not. In an earlier study in patients with recent onset RA, who had achieved sustained remission for at least one year, metacarpal BMD gain was found in 32% of patients.[7] These patients however achieved sustained remission for at least 1 year and later in the course of treatment after prolonged low disease activity, which may enable metacarpal BMD gain.

We found no differences in metacarpal BMD loss between UA and RA patients, although UA patients had a lower baseline disease activity at inclusion. This might be related to the similar symptom duration at study entrance and the fact that with the current treatment strategy disease activity was equally well suppressed during the first year in both groups.

A limitation of this study is the large amount of missing data. Radiographs were taken before we planned to measure DXR-BMD, and not for this purpose. To deal with this problem, we used multiple imputation, which is considered as a highly valid method to impute missing

data.[19] Results from the original dataset, although based on small numbers, showed similar trends.

In conclusion, during 1 year of remission steered therapy in patients with undifferentiated or early RA, metacarpal BMD loss seemed not to be influenced by disease activity, classification as RA or antibody status, but depends largely on age and postmenopausal status. Initial loss during treatment with a combination of methotrexate and a tapered high dose of prednisone may be substantial, and despite high remission rates and overall low disease activity, metacarpal BMD loss may only partially be recovered in the subsequent 8 months. These results may suggest that although initial combination therapy including a tapered high dose of prednisone may induce low disease activity and (sustained) remission in a large proportion of early arthritis patients, it may have at least a temporary negative effect on localized BMD.

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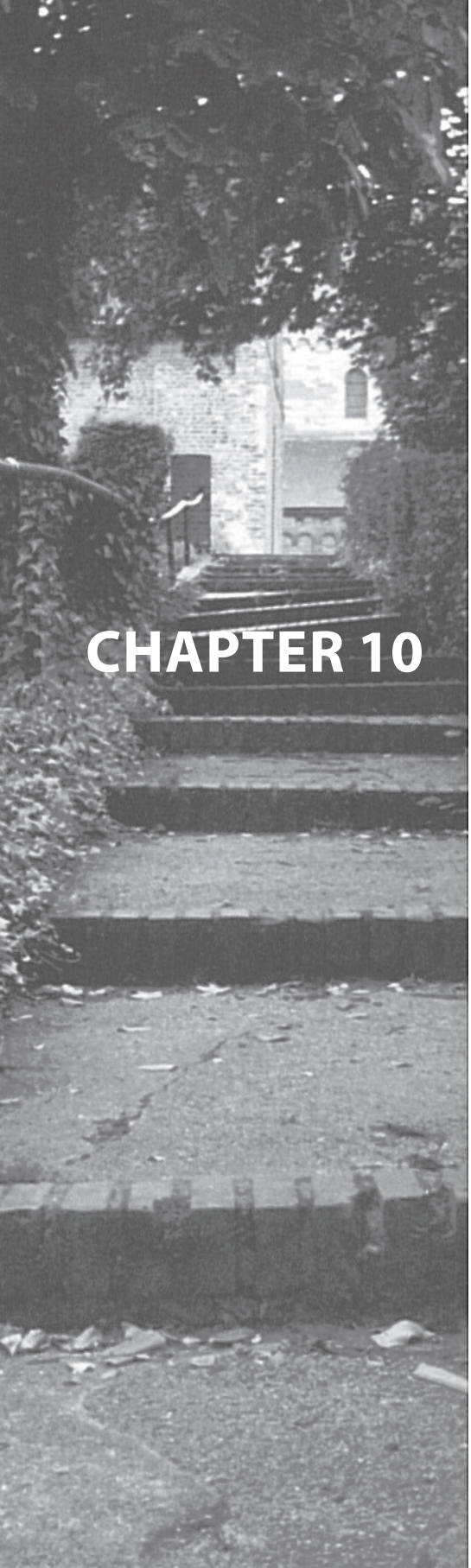

CHAPTER 10 Summary and conclusions

To date, only limited evidence is available to answer the question whether starting treatment already in the phase of undifferentiated arthritis (UA) is more effective than waiting until a patient meets classification criteria for rheumatoid arthritis (RA). As shown in chapter 2, the available evidence is not only limited, but there is also a huge heterogeneity in performed treatments and treatment strategies and in outcomes. Furthermore, the follow up duration of all trials is restricted and long term effects of the applied treatment strategies are not known.

The IMPROVED study, in which both patients with early RA and patients with UA were included, provides a valuable addition to the limited evidence for the beneficial effect of treating patients in early phases of RA, even before classification criteria are met.

THE IMPROVED STUDY: AN OVERVIEW OF OUTCOMES

In the IMPROVED study, patients with in an early phase of RA are intensively treated with combination treatment, introduced as early as in the phase of UA or early RA, and treatment is subsequently steered at the stringent goal of achieving remission. If remission was not achieved, medication was extended, either by adding more synthetic disease modifying anti-rheumatic drugs (DMARDs) to the initial treatment of prednisone and methotrexate (MTX), or by replacing prednisone with the biologic agent adalimumab. If remission was achieved medication was tapered, even until patients were in drug free remission. As early as one year after starting therapy, this goal was achieved in 20% of the patients. More than 50% of all patients were in remission and radiological damage progression was found in only 5% of the patients after one year. Also patient reported outcomes concerning functional ability and health related quality of life improved, and in a proportion of the patients even normalized, during the first year.

STUDY POPULATION

Inclusion

By protocol, DMARD-naïve patients with UA, defined as having at least one joint clinically diagnosed as arthritis and one other painful joint, not fulfilling the 1987 classification criteria for RA but in the opinion of the treating rheumatologist clinically suspect of early RA, and patients with early RA according to the 1987 criteria [1] and with a symptom duration of less than 2 years, were included. In chapter 3 is shown that, compared to previous clinical trials in patients with early RA, [2-5] we included patients with a relatively mild baseline disease activity (mean Disease Activity Score (DAS) 3.2), short symptom duration (median symptom duration 18 (9-32) weeks) and almost no radiological damage present (median baseline Sharp-van der Heijde Score (SHS) 0 (0-0) and 12% of the patients had erosions). Mean age (52 years)

and percentages female and rheumatoid factor (RF) positive patients (respectively 70% and 56%) were comparable with previous trials. The percentage of patients with a positive test for anti-citrullinated protein antibodies (ACPA) (55%) was also comparable with previous trials, although in most previous trials ACPA status was not known at baseline, but measured afterwards. As ACPA nowadays can be routinely measured in the Netherlands, rheumatologists were often aware of the ACPA status of patients they included in the IMPROVED study. This may explain why the percentage of ACPA positive patients was higher than one might expect in patients with early arthritis.

Reclassification

As in 2010 new ACR/EULAR classification criteria for RA were introduced,[6] we reclassified all patients participating in the IMPROVED study according to these new criteria. The new criteria aim to classify patients earlier in the disease course and give a lot of weight to the presence of ACPA and/or the presence of many arthritic joints. In chapter 3 we showed that 60% of the total study population fulfilled the 1987 classification criteria for RA and 40% were included as UA. Based on the new criteria 79% were classified as RA and 20% remained classified as UA. Thus, 19% of the patients were classified as RA by the 2010 criteria but not (yet) by the 1987 criteria. Compared to patients who were classified as RA according to the 1987 criteria,[1] these 19% had a comparable symptom duration, but they had a slightly lower baseline disease activity (mean DAS 3.3 versus 3.5), mainly due to a lower median swollen joint count (7 (3-11) versus 8 (4-12)) and a somewhat lower median erythrocyte sedimentation rate (ESR) level (26 (12-41) versus 29 (15-45). Other clinical variables were comparable.

In conclusion, compared to using the 1987 criteria, reclassification using the 2010 criteria did not result in identifying patients with a shorter symptom duration, but in classifying patients with a lower disease activity. Other studies, performed in early arthritis cohorts, showed similar results.[7,8] These findings seem to challenge some of the intentions of the new criteria.

Undifferentiated versus early rheumatoid arthritis

Although we expected that UA patients we included would have a shorter symptom duration than RA patients, this was not the case, as was shown in chapter 3. UA and RA patients had a median symptom duration of respectively 16 (8-28) and 18 (9-34) weeks. Included UA patients had lower baseline disease activity than RA patients (mean baseline DAS 2.7 (0.7) versus 3.3 (0.9)), and only a few UA patients were ACPA and/or RF positive compared to almost 70% of the RA patients. Another difference was apparent in the distribution of affected joints. Sixty-eight percent of UA patients and 73% of RA patients had involvement of large joints, but 6% of the UA patients had involvement of only large joints compared to none of the RA patients. UA patients with only large joint involvement might have had other

rheumatic diseases than RA, such as osteoarthritis or spondylarthropathy, in particular when ACPA and RF were negative.

ACPA negative patients who were still classified as RA differed from ACPA positive RA patients. To meet the 2010 classification criteria, ACPA negative RA patients had to have a higher disease activity than ACPA positive patients, mainly based on more affected joints. At time of classification, ACPA negative RA patients also had a longer symptom duration than ACPA positive RA patients.

MAIN OUTCOMES OF THE FIRST STUDY YEAR

Remission, drug free remission and joint damage progression

In chapter 3 we showed that, after 4 months of remission induction therapy with MTX and a tapered high dose of prednisone, as many as 61% of patients with early arthritis achieved remission (early remission, defined as DAS<1.6 [9]), regardless of fulfilling the 2010 criteria. Ninety percent of patients had no radiological progression and in those who had progression it was minimal (median progression score 1(1-1)). In chapter 4 we demonstrated that after one year of remission steered treatment, 54% of patients in the IMPROVED study were in remission and only 5% of the patients had radiological damage progression of more than 0.5 SHS points. Remission was most often achieved in patients who achieved early remission after four months (68%) and 32% of these patients were able to taper all medication and achieved drug free remission as soon as after one year. Patients who did not achieve early remission and were randomized, less often achieved remission after one year. Those randomized to treatment with MTX and adalimumab, with an increased dose of adalimumab as possible next step, more often achieved remission after one year (40%) than patients who were randomized to the extended combination of DMARDs with continued low dose prednisone, reserving adalimumab as possible next step (25%). Radiographic progression and functional ability were similar between randomization arms.

Compared to previous trials in patients with early RA, percentages of patients achieving remission during the first year of the IMPROVED study were high and joint damage was more effectively suppressed.[2,3,5,10,11] In other studies reporting similar high remission percentages after 1 year medication was not tapered.[11] On the other hand, these studies included patients with early or established RA with a higher baseline disease activity than patients in the IMPROVED study. Drug free remission was previously reported in 17-29% in clinical trials,[12-14] but never as soon as after one year. These results may be explained by the treatment strategy we used, starting early in disease course with combination therapy consisting of MTX 25 mg/week and a tapered high plus continued low dose of prednisone, followed by extending medication in those who did not achieve remission. Previously the beneficial effect of low dose corticosteroids compared to placebo was shown,[15] and several trials showed the benefit

of DMARD combination including prednisone compared to DMARD mono therapy.[2,3,5] In the recently published CAMERAII trial, a randomized placebo controlled trial in patients with early RA aimed at achieving remission, treatment with MTX was compared with MTX plus low dose prednisone. After 2 years of remission steered therapy, patients treated with MTX plus low dose prednisone had less radiological damage progression and more often and sooner achieved remission than patients treated with MTX alone. Remission percentages in this trial were comparable with percentages we found in the IMPROVED study, although in contrast with the IMPROVED study, there was no ability to taper medication as soon as remission was achieved.[16]

However, other explanations for the high (drug free) remission rates and nearly absence of radiological damage progression in the IMPROVED study may also be possible, such as the fact that early arthritis patients with a low disease activity at baseline may not have damage progression (yet) and may easier achieve the treatment goal of a DAS < 1.6. Also, some UA patients and patients who fulfilled the 2010 classification criteria may have had self-limiting forms of early arthritis, that would have gone into spontaneous remission without the use of medication.

Compared to the DAS-remission criteria that we used to steer treatment adjustments in the IMPROVED study, the Boolean based ACR/EULAR preliminary definition published in 2011 [17] appeared to be a more stringent definition, as fewer patients achieved remission according to this definition after 4 months (26%) and after 1 year (24%). In patients who were in DAS-remission but did not fulfill the Boolean based remission definition, this was most often due to a VAS global health ≥ 10. Recently, similar results were observed in the DREAM study,[18] in which also was shown that residual disease activity was only present in the minority (32%) of these patients. Thus, although the Boolean based definition is more stringent, the question raises whether it may be too stringent, resulting in patients in clinical remission not fulfilling this definition.

Never achieving remission during the first year

Results of chapter 4 showed that despite of the progressive treatment strategy aiming at remission, still 16% of patients did not achieve remission during the first year of treatment. Also, 5% of the patients had radiological damage progression after 1 year, although with a limited progression rate (median progression score of 1 and only one patient had rapid radiological progression of 18 SHS points). Patients who never achieved remission throughout the first year were characterized by a higher mean baseline disease activity (mean DAS 3.7 (0.9) versus 3.2 (0.9)), a longer symptom duration (24 (12-44) versus 17 (8-31) weeks) and included more females (89% versus 63%) compared to patients who achieved remission at least once. It is possible that these patients might have benefitted from starting treatment earlier when disease activity was still lower, or from treatment with other drugs. Follow up

therapy with other biologic therapies than adalimumab might have been more effective in these patients.[19]

Patient reported outcomes

In chapter 5 we showed that patient reported outcomes (PROs) at baseline, such as functional ability measured by the Health Assessment Questionnaire (HAQ) and McMaster Toronto Arthritis questionnaire (MACTAR) and health related quality of life measured by the Short Form-36 (SF-36), were lower in this population of early arthritis patients than in the general population. Only mental health, measured by the mental component score (MCS) of the SF-36, seemed not to be affected, since mean MCS in the IMPROVED study participants were comparable to the general population throughout the first year. During the first year, functional ability and physical health improved, with the greatest improvement occurring in the first four months. Improvement was largest in patients who achieved early remission. In this group, mean or median values of the HAQ and SF-36 after one year returned to levels comparable to those in the general population. In randomized patients, no differences were seen between treatment arms. In all patients, achieving remission during the first year was associated with better functional ability and health related quality of life than not achieving remission. These results suggest that with the current treatment strategy, PROs reflecting functional ability and physical health improve, and in part of the patients even normalize within one year after diagnosis. Achieving early remission after four months and achieving remission throughout the whole year improved PROs most.

Results of chapter 7 showed that minimal depressive symptoms were present among patients participating in the IMPROVED study. Depressive symptoms severity decreased with lower disease activity and was significantly lower in patients who achieve remission than in patients who did not. Mostly, this was due to symptoms of arthritis, such as pain and unwell being, rather than signs of inflammation, suggesting that depressive symptoms in RA patients may improve if symptoms of RA are optimally suppressed.

Metacarpal bone mineral density

In chapter 9 we explored changes in metacarpal bone mineral density (BMD) loss during the first year of remission steered treatment. The IMPROVED study is the first clinical trial in which metacarpal BMD was monitored this intensively and this early in the disease course of RA. These data however have to be interpreted with care, because they were imputed because of many missing values and most differences found were small. The data suggested that over half of the patients had metacarpal BMD loss after 4 months after 1 year (respectively 56% and 55%), and some patients might even have metacarpal BMD gain after 1 year (14%).

Our finding that more than half of these patients early arthritis, having a relatively mild disease activity and being treated intensively, may have had metacarpal BMD loss after 4 months, may be due to the initial treatment with a tapered high dose of prednisone. Only

a minority (13%) of the patients seem to totally regain this metacarpal BMD loss during the subsequent months. Longer follow data are needed to see whether this loss may be regained in the other patients in the second year or later. Another explanation may be the initial disease activity, although in these data, baseline disease activity was not found to be predictive of metacarpal BMD loss after 4 months.

The data may also suggest that patients who had achieved early remission and tapered medication, showed more metacarpal BMD loss than patients who were randomized to extended combination therapy. This may be explained by the intensive combination therapy randomized patients achieved, either including low dose prednisone or adalimumab. On the other hand, the fact that patients who achieved early remission tapered medication and that part of them lost remission, might also explain this possible difference. Although based on small numbers, the original data may furthermore suggest that patients treated with adalimumab may show the smallest loss in metacarpal BMD and most often metacarpal BMD gain after 1 year (54%, compared to 21% in patients randomized to combination therapy including prednisone and 12% of early remission patients). This is in line with previous research, showing that anti-TNF alpha inhibitors may reduce generalized as well as localized bone loss in patients with RA.[20-23]

Adverse events

Adverse events were reported in 56% of the patients during the first 4 months, as was shown in chapter 3. Most adverse events were mild and temporary, but in 3% of the patients serious adverse events occurred including the death of two patients, one of a pneumonia left untreated by wish of the patient and one of a myocardial infarction later found to be caused by a giant cell arteriitis. None of the serious adverse events were suspected unexpected serious adverse events (SUSARs). In general, initial combination therapy with MTX and a tapered high and continued low dose of prednisone appears to be safe on the short term. However, fourteen of sixteen serious adverse events (infections, cardiovascular disease, femoral head necrosis, diabetic complications) might have been related to the use of prednisone. Further follow up will show whether there are long term consequences of this induction therapy. Previous data of the COBRA trial, in which the same tapered high dose of prednisone was used, suggest that a tapered high dose of prednisone, in combination with MTX and SSZ, can be used safely.[2,24] Previously, no evidence has been found for long term complications of short term use of low dose prednisone.[15]

In chapter 4 we showed that from 4 months two one year adverse events were reported in 57% of the patients. The lowest percentage of adverse events was reported in the early remission group (53%) and adverse events were reported in similar percentages in the randomization arms (74% in arm 1 and 68% in arm 2). Adverse were generally mild. Serious adverse events were reported in 4% of the patients, including 3 patients who died; one of a squamous cell carcinoma of the tongue (early remission group), one of a cerebral tumor (arm

2) and one of an ovarian carcinoma (OP group). Serious adverse events that were possibly related to the use of adalimumab were: pneumonia, cerebral tumor, percutaneous coronary intervention for myocardial infarction, exacerbation of chronic obstructive pulmonary disease and cerebrovascular accident. None of the serious adverse events were SUSARs. In summary, also after 1 year, adverse events were generally mild and combination treatment with multiple DMARDs and low dose prednisone seemed to be equally safe as treatment with MTX and adalimumab.

LIMITATIONS OF THE IMPROVED STUDY

No control group

To avoid the need of excessive patient numbers, no control group was included in the IMPROVED study to verify the superiority of the initial combination treatment. Instead of finding the best initial treatment, we decided to use a combination of two drugs, proven very effective as initial treatment for patients with active RA,[2,3] in all patients and focus on identifying the best follow up treatment when the initial treatment did not result in remission. This means we also do not know how many UA and RA patients would actually have achieved remission spontaneously and thus which part achieved remission and drug free remission due to the applied therapy.

Single blind study

This study was a single blind study. For practical reasons, only research nurses who did the four monthly assessments were blinded, while patients and doctors were aware of the allocated treatment. Several years after the introduction of biological agents, patients participating in the BeSt study were shown to have a preference for combination therapy including infliximab and disliked taking prednisone.[35] In the IMPROVED study, patients might also have had a preference for combination therapy including a biological agent, in this case adalimumab, which might have biased our results. However, almost none of the patients randomized to the combination of multiple DMARDs and low dose prednisone refused to start with this therapy.

Definition of remission: DAS <1.6

Remission was defined as a DAS <1.6 and treatment was steered at this definition. In the past, it has been shown to correspond well to the 1981 ACR preliminary criteria for clinical remission.[9,36] However, because this definition allows for one or two swollen or painful joints, some say that it reflects low disease activity rather than remission. Recently two new definitions for remission have been proposed.[37] In the IMPROVED study, the Boolean based definition for remission [17] appeared to be more stringent than the DAS-definition. In future,

one of the provisional definitions may best be used to reach uniformity among clinical trials. However, it remains questionable whether the various remission definitions are associated with significant differences in clinical and radiological outcomes.[38]

Protocol deviations

Protocolized treatments adjustments in the IMPROVED study were integrated in daily practice, which led to a considerable amount of protocol deviations for several reasons. Sometimes the treating rheumatologist disagreed with the required treatment step or with the DAS evaluation by the research nurse. For example, a DAS might have been high due to an elevated ESR or painful joints due to other reasons than RA activity. In this case rheumatologist deviated from the protocol because the patient was clinically in remission. Also, the fact that we steered at remission defined as a DAS <1.6 might have caused protocol deviations. When for example the DAS was 1.6 or just >1.6, treatment had to be intensified according to the protocol but sometimes rheumatologists hesitated to do so. Or sometimes they might have hesitated to taper medication when the DAS was <1.6 but they felt there still was some residual disease activity.

In 50 patients who did not achieve remission after 4 months, the protocol was not followed and patients were not randomized (Outside of Protocol group, OP group). In 17 of these patients prednisone was tapered, probably because these patients were estimated by the rheumatologist to be in clinical remission, but the DAS was >1.6 due to other reasons. In other patients several other treatment steps were taken for different reasons. In most cases treatment remained steered at remission, but this was clinical rather than DAS-remission. After 1 year, outcomes of the patients in the OP group were similar to patients who had been randomized to arm 1, suggesting that following the current treatment strategy may lead to better disease outcomes than treatment outside of protocol.

UA VERSUS RA

We included UA patients 'clinically suspect for RA' because we expected that these patients would represent RA patients with a shorter disease duration than classifiable RA patients and might achieve remission in a higher rates. This would support the window of opportunity theory.[25,26] Our results in chapter 3 however showed that UA patients did not have shorter symptom duration at inclusion of the study than RA patients (median (IQR) 16 (8-28) versus 18 (9-34) weeks, respectively). It is thought that the first twelve weeks after symptom onset offer the best opportunity to stop or reverse the disease process that otherwise may become chronic and destructive. This means that for 64% of the UA patients as well as for 66% of the RA patients with a symptom duration ≥ 12 weeks, the window of opportunity may have been missed.

UA patients also may have had a favorable outlook compared to the RA patients because on average they were included with a lower disease activity, and almost all were auto-antibody negative, possibly including patients with self-limiting forms of arthritis. However, as shown in chapters 3 and 4, we found no differences between UA and RA patients in percentages (drug free) remission, functional ability or radiological joint damage progression after 4 months or 1 year. Besides having missed the window of opportunity, some UA patients may not have had self-limiting arthritis but rather a type of rheumatic disease that did not respond to the given therapy (for example osteoarthritis or spondylarthropathy).

PRESENCE VERSUS ABSENCE OF ANTI-CITRULLINATED PROTEIN ANTIBODIES

The presence of ACPA is known as a factor associated with a higher disease activity, more functional disability and more radiological damage progression in patients with RA.[27-29] Therefore we were surprised to find that after one year in the IMPROVED study, as described in chapter 6, ACPA positive patients achieved remission and drug free remission equally often as ACPA negative patients and also functional ability and radiological damage progression both were similar in ACPA positive and negative patients. After the initial combination therapy of MTX and a tapered high dose of prednisone, ACPA positive patients even achieved remission more often than ACPA negative patients. This might suggest that ACPA positive patients responded better to the initial combination therapy than ACPA negative patients. Previously, results of the PROMPT study showed that in ACPA negative UA patients MTX was not superior to placebo treatment, while in ACPA positive patients MTX resulted in suppression of progression to classifiable RA and suppression of joint damage progression.[30,31] This suggests that ACPA negative UA responds less well to anti-inflammatory treatment than ACPA positive UA, and therefore may be driven by different disease pathways.

Furthermore, results of chapter 6 showed that of those patients who achieved early remission, and by protocol of the IMPROVED study were able to achieve drug free remission (DFR) after 1 year, 32% actually achieved DFR after 1 year. Of those, 55% were ACPA positive, compared to 61% of the patients who achieved early remission but not DFR after 1 year (no significant difference). Patients in DFR after 1 year were less often RF factor positive than patients not achieving DFR (50% versus 62%).

In the following 4 months, 30% of the patients who had achieved DFR after 1 year, lost it. These patients were more often ACPA positive than patients who did not lose DFR (72% versus 47%), and ACPA positive patients less often sustained DFR than ACPA negative patients (58% versus 80%). This suggests that compared to ACPA negative patients, ACPA positive patients have a similar likelihood of achieving and maintaining remission, even while medication is tapered. But after having successfully tapered and discontinued medication, ACPA positive patients show more relapses in disease activity in the next 4 months.

PREDICTION OF DISEASE OUTCOME BY METACARPAL BONE MINERAL DENSITY

We showed in chapter 8 that metacarpal bone mineral density (BMD) loss in the first 4 months after diagnosis was predictive for radiological damage progression after 1 year of remission steered treatment in the IMPROVED study, independent of several known predictors. The presence of baseline erosions was found to be the only other predictor, but 86% of the total study group had no erosions at baseline and 17 (5%) still developed radiological progression (63% of all 27 patients with radiological progression). In patients without baseline erosions no predictors other than metacarpal BMD loss after 4 months were found.

Preferably, an outcome predictor would be present at baseline. But with the lack of baseline predictors, especially in patients without baseline erosions, and with achieving remission after 4 months also not being predictive for future joint damage, metacarpal BMD loss after 4 months may be a useful new predictor in patients with early arthritis.

Furthermore, several known predictors of (rapid) radiological progression, such as ACPA and/or RF positivity and baseline CRP or ESR level, were not found to be predictive of progression in this population with almost no progression present after 1 year. This may be explained by the treatment strategy we applied, starting early in disease course with combination treatment and steering at remission, which may have prevented progression of radiological damage. But it may also be possible that radiological progression would, also without medication, hardly be present in this early arthritis population with a relatively low disease activity.

In conclusion, early metacarpal BMD loss may be used in clinical practice or may be added to known prediction models of disease outcome in patients with RA [32-34] to steer early treatment decisions with the ultimate goal of preventing radiological joint damage.

FUTURE PERSPECTIVES

Data in this thesis suggest that, with the treatment strategies applied in the IMPROVED study, disease outcomes have indeed been further improved in early phases of RA. Remission and even drug free remission can be achieved in higher proportions of patients and earlier in disease course than before. Future results of the IMPROVED study will show for how long and in which patients remission and drug free remission can be sustained, if tapering of medication and achieving drug free remission is also possible in patients who were randomized, how many and which patients will have radiological progression, and what will be the best follow up treatment strategy in patients who did not achieve remission within the first year. After one year, remission was achieved in approximately half of the patients, of which about one third were in drug free remission. To achieve these goals in the majority, or ultimately even in all patients, treatment strategies still need further optimization.

Even including results of the IMPROVED study, the current evidence of treating patients in the stage of undifferentiated arthritis is limited and very heterogeneous. Further research has to elucidate the optimal period to start treatment and the optimal treatment strategy. Starting therapy within twelve weeks after symptom onset may further improve outcomes, but may also increase overtreatment of patients with a self-limiting type of arthritis. In these patients, tapering medication as soon as remission is achieved may further minimize the risk of side effects.

Targeting treatment to low disease activity has been shown to benefit patients with RA and our results as well as data from the FINRA-Co and NEORA-Co study suggest that remission as treatment target may be even better. However, a randomized trial with a head to head comparison of the same treatment strategy aiming either at low disease activity or at remission has not been done. Until such as trial has been performed, no definitive statement can be made on the superiority of remission over low disease activity as treatment goal.

Adding short term prednisone to one or more DMARDs may become a new cornerstone in the treatment of RA. It has been shown to suppress disease activity and radiological damage as effectively as combination therapy including a biologic agent, but may offer a less expensive alternative. However, the optimal dosage and duration of therapy has still to be determined and future research has to ensure that short and long term side effects are indeed acceptable.

In patients who do not achieve remission on initial DMARD therapy in combination with prednisone, follow up treatment with early introduction of a biological agent seems to result in more patients achieving remission. Whether drug free remission is also achieved more often en whether damage progression is more effectively suppressed still has to be determined. If this is the case, exchanging prednisone for a biologic agent in these patients may be the best next step in their treatment strategy.

There is an ongoing search for new predictors to further optimize current prediction models for disease outcome in patients with RA. Early bone loss may be a candidate for further improvement of predicting the disease course in individual patients. To improve prediction even more, future research has to reveal more new predictor candidates. Being able to accurately predict disease outcome in all patients with RA will offer the best opportunity to choose the most advantageous treatment strategy for all individual patients.

In conclusion, the current treatment strategy, including early start of combination therapy and steering treatment at remission, may have contributed to the high remission and drug free remission rates and the nearly absence of radiological damage progression after one year in patients with early arthritis. However, current treatment strategies still need further optimization with the ultimate goal of achieving these outcomes in the future in every patient in an early phase of RA.

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Nederlandse samenvatting

VERBETERING VAN ZIEKTE-UITKOMSTEN IN EEN VROEGE FASE VAN REUMATOÏDE ARTRITIS

Reumatoïde artritis (RA) is een potentieel invaliderende auto-immuunziekte die gekenmerkt wordt door symmetrische gewrichtsontstekingen waarbij hand- en voetgewrichten meestal betrokken zijn. De behandeling van RA heeft de afgelopen decennia een enorme verandering doorgemaakt. Vele onderzoeken hebben aangetoond dat het behandelen van patiënten vroeg in het ziektebeloop, zo snel mogelijk na het stellen van de diagnose, betere ziekte-uitkomsten geeft. In 2010 hebben de European League Against Rheumatism (EULAR) en de American College of Rheumatology (ACR) gezamenlijk nieuwe classificatie criteria voor RA ontworpen, met als doel patiënten vroeger in het ziektebeloop te classificeren, zodat behandeling eerder kan worden gestart. Ook het behandelen met een combinatie van middelen in plaats van monotherapie heeft geleid tot een snellere onderdrukking van ziekteverschijnselen, minder gewrichtsschade en minder invaliditeit. Verder heeft de ontdekking van relatief nieuwe middelen, biologicals genaamd, bijgedragen aan de verbetering van ziekte-uitkomsten. Tot slot is gebleken dat het streven naar lage of geen meetbare ziekte activiteit, door patiënten intensief te vervolgen en medicatie zo nodig aan te passen ('tight control'), heeft bijgedragen aan deze vooruitgang.

Het gevolg is dat de ziekte RA, voorheen bekend als een chronische en invaliderende aandoening, steeds minder vaak een chronisch beloop kent en dat symptomen steeds beter en vroeger in het ziektebeloop onderdrukt kunnen worden in het merendeel van de patiënten. Het behalen van remissie en zelfs medicatie vrije remissie zijn haalbare behandeldoelen geworden die in toenemende aantallen patiënten worden bereikt.

Deze enorme verbetering in prognose roept echter de vraag op of de ziekte niet nóg beter, nóg eerder en in nóg meer patiënten kan worden onderdrukt. Mogelijk leiden behandeling in het stadium dat patiënten nog niet aan de classificatie criteria voor RA voldoen, sturen van behandeling op remissie in plaats van op lage ziekte activiteit en combinatie behandeling met prednison of een biological vroeg in het ziekte-beloop, tot een verdere verbetering van ziekte-uitkomsten. De ultieme vraag is zelfs of, met de juiste behandeling op het juiste tijdstip, genezing kan worden bereikt.

In dit proefschrift, waarin resultaten van het eerste jaar van de Induction therapy with Methotrexate and Prednisone in Rheumatoid Or Very Early arthritic Disease (IMPROVED) studie worden getoond, hopen we een stap dichter bij de beantwoording van bovenstaande vragen te komen. In dit hoofdstuk worden de belangrijkste uitkomsten samengevat en bediscussieerd.

BEHANDELING VAN ONGEDIFFERENTIEERDE ARTRITIS

Het wetenschappelijk bewijs voor het effect van behandeling in het stadium van ongedifferentieerde artritis (UA) is nog maar zeer beperkt, zo blijkt uit een systematische review van studies over behandeling van patiënten met UA (*hoofdstuk 2*). Het aantal studies is klein, onderzochte behandelingen of behandelstrategieën en uitkomsten zijn zeer heterogeen, en de effecten van behandeling zijn uitsluitend op korte termijn geëvalueerd.

Met de IMPROVED studie, waarin zowel patiënten met vroege RA als patiënten met UA geïncludeerd zijn, wordt zeer waardevolle kennis toegevoegd aan het beperkt aanwezige bewijs dat starten van behandeling nog voordat patiënten voldoen aan de classificatie criteria voor RA zinvol is.

DE IMPROVED STUDIE

De IMPROVED studie is een gerandomiseerde klinische studie waarin patiënten met UA en met vroege RA zijn geïncludeerd. RA is gedefinieerd als voldoend aan de ACR 1987 classificatie criteria voor RA, UA als hebbende op zijn minst één gewricht met artritis en één ander pijnlijk gewricht, zonder aanwijzingen voor een andere reumatologische aandoening. Patiënten zijn behandeld volgens een 'tight control' strategie, waarbij behandeling gestuurd is op remissie, gedefinieerd als een ziekteactiviteit score ('Disease Activity Score', DAS) < 1.6. Alle patiënten werden initieel behandeld met methotrexaat (MTX) 25 mg/week en prednison 60 mg/dag, in 7 weken afgebouwd tot 7.5 mg/dag. Patiënten die met deze initiële behandeling remissie bereikten, bouwden eerst prednison geheel af. Patiënten die hierna remissie behielden, bouwden 4 maanden later ook MTX geheel af. Binnen een jaar na het starten van medicatie kon zo medicatie vrije remissie worden bereikt. Patiënten die remissie niet behielden na het afbouwen van prednison, herstartten prednison 7.5 mg/dag.

Patiënten die geen remissie bereikten na de initiële behandeling, werden gerandomiseerd in twee armen. In arm 1 werden twee anti-reumatische middelen ('Disease Modifying Anti-Rheumatic Drugs', DMARDs), sulfasalazine (SSZ) en hydroxychloroquine (HCQ), toegevoegd aan MTX en prednison; in arm 2 werd prednison vervangen door de biological adalimumab en werd MTX gecontinueerd.

De belangrijkste ziekte-uitkomsten zijn remissie, medicatie vrije remissie en progressie van gewrichtsschade. Andere uitkomsten zijn onder andere patiënt gerapporteerde uitkomsten ('patient reported outcomes', PRO), zoals dagelijks functioneren en ziekte gerelateerde kwaliteit van leven.

Inclusie en reclassificatie

In totaal zijn 610 patiënten geïncludeerd in de IMPROVED studie, waarvan 60% voldeed aan de 1987 criteria voor RA (*hoofdstuk 3*). Na publicatie van de 'nieuwe' 2010 criteria zijn patiënten opnieuw geclassificeerd, waarbij 79% voldeed aan de 2010 classificatie criteria (RA patiënten) en 20% niet (UA patiënten) (1% van de patiënten was niet classificeerbaar door missende waarden). UA patiënten bleken niet, zoals verwacht, een kortere symptoomduur te hebben, maar hadden ten tijde van de inclusie een lagere ziekteactiviteit dan RA patiënten. Ook waren reumafactoren (RF) en antistoffen tegen gecitrullineerde eiwitten ('Anti-Citrullinated Protein Antibodies', ACPA) in slechts enkele UA patiënten aanwezig, vergeleken met 70% aanwezigheid van deze antistoffen in RA patiënten.

Remissie, medicatie vrije remissie en schade progressie

Na 4 maanden behandeling met MTX en prednison bereikten 61% van de patiënten remissie (vroege remissie), waarbij de remissie percentages niet verschilden tussen RA en UA patiënten (*hoofdstuk 3*). Negenentwintig procent van de patiënten bereikten geen vroege remissie en werden gerandomiseerd, 83 in arm 1 (MTX, SSZ, HCQ en lage dosering prednison) en 78 in arm 2 (MTX en adalimumab), en 50 (8%) patiënten bereikten geen remissie maar werden niet gerandomiseerd volgens het studieprotocol (*hoofdstukken 3 en 4*). Zeventien van deze patiënten waren volgens de reumatoloog klinisch in remissie, waarna werd gestart met het afbouwen van prednison. In de overige patiënten werd het protocol om verschillende andere redenen niet gevolgd.

Na een jaar waren van alle patiënten 54% in remissie en 20% zelfs in medicatie vrije remissie. In slechts 5% van de patiënten was radiologische progressie aanwezig. Met een mediane Sharp van der Heijde progressie score (SHS) van 1 was de mate van progressie minimaal. Slechts 1 patiënt had een progressie score ≥ 5 (18 punten). Er waren geen verschillen tussen patiënten met UA en RA. Patiënten die na 4 maanden remissie bereikten, waren na 1 jaar het meest frequent in remissie (68%). Van hen behaalden 32% medicatie vrije remissie. Patiënten die gerandomiseerd waren voor behandeling met MTX en adalimumab bereikten vaker remissie na 1 jaar dan patiënten die gerandomiseerd waren voor MTX, SSZ, HCQ en lage dosering prednison (41% versus 25%). De hoeveelheid radiologische schade na 1 jaar verschilde niet tussen de randomisatie armen.

Vergeleken met eerder onderzoek worden remissie en medicatie vrije remissie in het eerste jaar van de IMPROVED studie in hoge percentages bereikt en wordt radiologische progressie zeer goed onderdrukt. In enkele voorgaande studies zijn vergelijkbaar hoge remissie percentages bereikt, maar medicatie is in deze studies niet afgebouwd dan wel gestopt. Wel zijn over het algemeen patiënten met een hogere ziekte activiteit geïncludeerd. Medicatie vrije remissie is in eerdere studies beschreven in 17-29%, maar nooit eerder zijn deze percentages binnen 1 jaar na het starten van medicatie bereikt.

De resultaten kunnen worden verklaard door de intensieve, remissie gestuurde behandeling, die patiënten in de IMPROVED studie al vroeg in het ziektebeloop hebben gekregen. In voorgaand onderzoek zijn de positieve effecten van behandeling met lage dosering prednison ten opzichte van placebo in RA patiënten aangetoond, evenals de positieve effecten van combinatie therapie met lage dosering prednison ten opzichte van monotherapie. De recent gepubliceerde, gerandomiseerde en placebo gecontroleerde CAMERAII studie toont tevens aan dat remissie gestuurde behandeling met MTX en lage dosering prednison superieur is aan MTX monotherapie, waarbij het bereikte percentage remissie na 2 jaar vergelijkbaar is met het behaalde percentage remissie na 1 jaar in de IMPROVED studie.

Maar er zijn meerdere verklaringen mogelijk voor onze resultaten. Omdat patiënten vroeg in het ziektebeloop en met een relatief lage ziekte activiteit zijn geïncludeerd, wordt het behandeldoel remissie (ofwel een DAS < 1.6) wellicht makkelijker bereikt en is schade progressie misschien nog nauwelijks aanwezig. Ook kan de vroege inclusie hebben geleid tot deelname van patiënten die ook spontaan remissie zouden hebben bereikt, zonder enige vorm van behandeling.

In 2011 is door de ACR en EULAR een voorstel gedaan voor nieuwe remissie criteria in klinische trials, omdat er tot dan toe geen uniforme definitie voor remissie voorhanden was en omdat een aantal huidige definities eerder lage ziekteactiviteit dan remissie vertegenwoordigen. Een van de twee voorgestelde definities is de zogenaamde 'Boolean based' definitie. In de IMPROVED studie bereikten na 4 maanden en na 1 jaar respectievelijk 26% en 24% van de patiënten remissie volgens deze definitie (*hoofdstukken 3 en 4*). Het merendeel van de patiënten die in remissie waren volgens de DAS definitie maar niet volgens de Boolean based definitie, bereikten geen remissie omdat de visueel analoge schaal (VAS) voor globale ziekte activiteit als enig criterium verhoogd was (≥ 10 mm op een schaal van 100 mm). Vergelijkbare resultaten zijn recentelijk ook in de DREAM studie gezien, waarbij een deel van deze patiënten klinisch wel in remissie bleken te zijn. De Boolean based definitie lijkt dus een striktere definitie te zijn dan de DAS definitie, maar is wellicht te strikt, waardoor een deel van de patiënten die klinische in remissie zijn, wellicht volgens deze definitie niet in remissie zijn.

Geen remissie tijdens het eerste studie jaar

Ondanks goede resultaten in het merendeel van de patiënten, bereikten 16% van de patiënten op geen enkel moment tijdens het eerste studie jaar remissie, zoals beschreven in *hoofdstuk 4*. Deze patiënten werden gekenmerkt door een hogere ziekte activiteit aan het begin van de studie (gemiddelde DAS 3.7 (0.9) versus 3.2 (0.9)), een langere symptoomduur (mediane duur 24 (12-44) versus 17 (8-31) weken) en ze waren vaker vrouw (89% versus 63%) vergeleken met patiënten die een of meerdere keren remissie bereikten. Wellicht hadden deze patiënten baat gehad bij het starten van behandeling in een vroegere fase of bij andere medicatie, bijvoorbeeld een andere biological dan adalimumab.

Patiënt gerapporteerde uitkomsten

Resultaten in *hoofdstuk 5* laten zien dat het dagelijks functioneren (gemeten met de Health Assessment Questionnaire, HAQ) en de ziekte gerelateerde kwaliteit van leven (gemeten met de Short Form-36, SF-36) in deze populatie met vroege artritis lager is dan in de normale populatie. Ziekte gerelateerde kwaliteit van leven kan onderverdeeld worden in mentale en fysieke gezondheid, waarbij alleen de fysieke component aangedaan bleek te zijn in patiënten in de IMPROVED studie. Na 1 jaar behandeling waren zowel het dagelijks functioneren als de fysieke gezondheid in de totale studie groep verbeterd. De grootste verbetering vond plaats in patiënten die vroege remissie bereikten, waarbij na 1 jaar gemiddelde waarden gemeten werden die vergelijkbaar waren met die in de normale populatie. In gerandomiseerde patiënten werd geen verschil gezien tussen de randomisatie armen. Het bereiken van remissie gedurende het eerste jaar was geassocieerd met beter dagelijks functioneren en betere ziekte gerelateerde kwaliteit van leven. Concluderend leidt het bereiken van remissie en in het bijzonder van vroege remissie, tot de grootste verbetering en in een deel van de patiënten zelfs tot normalisatie van dagelijks functioneren en ziekte gerelateerde kwaliteit van leven in patiënten met vroege RA.

Resultaten in *hoofdstuk 7* laten zien dat patiënten met vroege artritis weinig depressieve symptomen hebben. De ernst van depressieve symptomen daalde wanneer patiënten een lagere ziekte activiteit hadden en het behalen van remissie resulteerde in significant minder depressieve klachten. Depressieve klachten traden voornamelijk op door symptomen van artritis, zoals pijn en malaise. Dit suggereert dat depressieve symptomen het beste kunnen worden tegengegaan door het optimaal behandelen van symptomen van artritis.

Afname van metacarpale botdichtheid

Viermaandelijkse metingen van botmineraaldichtheid (BMD) in de metacarpalen tijdens het eerste jaar van de IMPROVED studie suggereren dat ruim de helft van de patiënten een afname van metacarpale BMD had (metacarpaal BMD verlies) na 4 maanden en na 1 jaar (respectievelijk 56% en 55%) *(hoofdstuk 9)*. Mogelijk was er bij sommige patiënten ook sprake van een toename van metacarpaal BMD na 1 jaar (14% van de patiënten). Aangezien deze resultaten gebaseerd zijn op geïmputeerde data en de geobserveerde verschillen soms klein zijn, dienen ze met voorzichtigheid geïnterpreteerd te worden.

Het feit dat mogelijk ruim de helft van de patiënten met vroege artritis, ondanks een relatief lage ziekte activiteit, metacarpaal BMD verlies had na 4 maanden van vroege en intensieve behandeling, kan wellicht verklaard worden door de tijdelijke hoge dosering prednison waarmee ze behandeld zijn. Slechts een kleine deel van de patiënten (13%) leek het totale verlies (of meer) tijdens de daarop volgende maanden weer te herwinnen. Uit data met een langere follow up duur zal duidelijk moeten worden of het metacarpaal BMD verlies zich ook bij de overige patiënten nog hersteld. Ook de initiële ziekte activiteit kan hebben bijgedragen aan het hoge percentage patiënten met metacarpaal BMD verlies, hoewel de

resultaten suggereren dat ziekte activiteit bij aanvang van de studie geen voorspeller is van metacarpaal BMD verlies na 4 maanden.

Patiënten die na 4 maanden vroege remissie bereikten en medicatie afbouwden, leken na 1 jaar meer metacarpaal BMD verlies te hebben dan patiënten die werden gerandomiseerd. Dit kan verklaard worden door de intensieve combinatie therapie met lage dosering prednison dan wel met adalimumab, waarmee gerandomiseerde patiënten werden behandeld. Maar ook het feit dat patiënten die vroege remissie bereikten medicatie afbouwden, en dat een deel van hen remissie verloor, kan hebben bijgedragen.

Hoewel gebaseerd op kleine aantallen patiënten, suggereren de resultaten dat met adalimumab behandelde patiënten het kleinste metacarpaal BMD verlies hadden en het meest frequent een toename van metacarpale botdichtheid na 1 jaar (54%, vergeleken met 21% van de gerandomiseerde patiënten behandeld met combinatie therapie met lage dosering prednison en 12% van de patiënten in vroege remissie). Dit is in lijn met eerder onderzoek, waaruit is gebleken dat behandeling met anti-TNF-α middelen mogelijk gegeneraliseerde en lokale afname van botdichtheid remt.

Bijwerkingen

Na 4 maanden behandeling met MTX en prednison werden in 56% van de IMPROVED patiënten bijwerkingen gerapporteerd (*hoofdstuk 3*). De meeste bijwerkingen waren mild en tijdelijk van aard, maar in 3% van de patiënten was er sprake van ernstige bijwerkingen. Twee patiënten overleden, een ten gevolge van een pneumonie (waarvoor patiënte niet behandeld wenste te worden) en een ten gevolge van een myocard infarct, dat bij obductie veroorzaakt bleek te zijn door een reuscel arteriitis van de coronair arteriën. Veertien van de 16 ernstige bijwerkingen werden mogelijk veroorzaakt door prednison (infecties, hart en vaat ziekten, kopnecrose van de heup, diabetische complicaties).

Na 1 jaar behandeling in de IMPROVED werden in 57% van de patiënten bijwerkingen gerapporteerd (*hoofdstuk 4)*. In patiënten die vroege remissie bereikten en vervolgens medicatie afbouwden, werden de minste bijwerkingen gerapporteerd (53%). Er werd geen verschil gezien in bijwerkingen tussen de randomisatie armen (74% in arm 1 and 68% in arm 2). In 4% van de patiënten vonden ernstige bijwerkingen plaats. Drie patiënten overleden, allen ten gevolgen van een maligniteit: een plaveiselcel carcinoom van de tong (vroege remissie groep), een hersentumor (arm 2: MTX+adalimumab) en een ovariumcarcinoom (in vroege remissie maar niet gerandomiseerd volgens protocol). Ernstige mogelijk aan prednison gerelateerde bijwerkingen waren: pneumonie, hersentumor, percutane coronaire interventie in verband met een hartinfarct, exacerbatie van 'chronic obstructive pulmonary disease' (COPD) op basis van een luchtweginfectie en een cerebrovasculair accident (CVA).

Concluderend lijkt de initiële behandeling met MTX en prednison op korte termijn veilig te zijn. In het vervolg van de IMPROVED studie zullen ook lange termijn gevolgen van prednison geëvalueerd worden (5 jaar follow up). Voorgaand onderzoek heeft tot nu toe geen lange

termijn complicaties laten zien van kortdurende behandeling met lage dosering prednison. Verder suggereren de resultaten dat er geen verschil in bijwerkingen is tussen behandeling met een combinatie van DMARDs met een lage dosering prednison en behandeling met MTX in combinatie met adalimumab.

BEPERKINGEN VAN DE IMPROVED STUDIE

Om de grootte van de studie te beperken, is er in de IMPROVED studie geen controle groep geïncludeerd om uitkomsten van de initiële behandeling met MTX en prednison te kunnen vergelijken met placebo. In voorgaand onderzoek is aangetoond dat combinatie behandeling met MTX en prednison zeer effectief is in patiënten met RA. Daarom is ervoor gekozen om de optimale vervolg strategie te onderzoeken in een gerandomiseerde vervolg fase van het onderzoek. Door het ontbreken van een controle groep kan er geen uitspraak worden gedaan over hoeveel patiënten zonder behandeling remissie zouden hebben bereikt.

Wegens praktische redenen zijn alleen de onderzoeksverpleegkundigen, die viermaandelijkse uitkomsten zoals DAS en HAQ evalueerden, geblindeerd voor de gegeven behandeling. Artsen en patiënten waren zich hiervan wel bewust. Kort na de introductie van biologicals is in de BeSt studie beschreven dat patiënten een voorkeur hadden voor behandeling met een biological en een afkeur tegen prednison. Resultaten van de IMPROVED studie zouden dus vertekend kunnen zijn door het feit dat patiënten en artsen op de hoogte waren van de gegeven behandeling. Patiënten weigerden echter zelden de medicatie waarvoor zij geloot hadden.

In de IMPROVED studie is remissie gedefinieerd als een DAS <1.6. Voorgaand onderzoek heeft aangetoond dat deze definitie correspondeert met de in 1981 door de ACR opgestelde criteria voor klinische remissie. Er wordt echter gedacht dat een DAS <1.6 eerder lage ziekteactiviteit dan remissie representeert, omdat patiënten die aan deze definitie voldoen maximaal twee gezwollen of pijnlijke gewrichten kunnen hebben. De in 2011 voorgestelde nieuwe definities voor remissie zijn na het starten van de IMPROVED studie gepubliceerd. In de toekomst is meer onderzoek nodig naar de validiteit van de nieuwe definities en zal moeten blijken of de verschillende definities gepaard gaan met verschillen in ziekte-uitkomsten zoals dagelijks functioneren en radiologisch schade progressie.

Tot slot is tijdens het eerste jaar van de IMPROVED studie relatief frequent afgeweken van het studieprotocol. Dit is waarschijnlijk veroorzaakt door het feit dat de geprotocolleerde behandeling van studie patiënten is geïntegreerd in de dagelijkse klinische praktijk. De behandelende reumatologen waren het soms oneens met de DAS verricht door de onderzoeksverpleegkundige, of beoordeelden dat de DAS verhoogd was door een andere oorzaak dan ziekteactiviteit van RA. In dat geval weken ze af van het studie protocol omdat de patiënt klinisch in remissie was. Ook het feit dat behandeling gestuurd werd op een DAS <1.6 kan

hebben geleid tot protocol afwijkingen, bijvoorbeeld omdat een arts aarzelde om medicatie aan te passen als de DAS slechts minimaal hoger of lager dan 1.6 was.

Vijftig patiënten zijn na 4 maanden niet in een behandelgroep worden ingedeeld omdat ze geen remissie bereikten maar ook niet volgens protocol gerandomiseerd werden. Ze zijn daarom als aparte groep geanalyseerd. Ziekte-uitkomsten in deze groep patiënten waren na 1 jaar vergelijkbaar met patiënten in arm 1 (DMARDs en een lage dosering prednison), maar waren wellicht beter geweest wanneer deze patiënten wel volgens protocol waren behandeld.

UA VERSUS RA

Naar verwachting hebben UA patiënten een kortere symptoomduur en bereiken ze vaker remissie dan patiënten met vroege RA. De symptoomduur van UA en RA patiënten ten tijde van inclusie in de IMPROVED was echter vergelijkbaar (mediane duur 16 (8-28) versus 18 (9-34) weken). Vierenzestig procent van de UA patiënten en 66% van de RA patiënten hadden een symptoomduur langer dan 12 weken. Volgens de zogenaamde 'window of opportunity' theorie kan de juiste behandeling tijdens de 'window of opportunity', waarvan is geopperd dat deze de eerste 12 weken na het ontstaan van klachten beslaat, voorkomen dat klachten chronisch worden en de ziekte destructief wordt.

Ondanks het feit dat UA patiënten bij inclusie een lagere ziekteactiviteit hadden vergeleken met RA patiënten en dat autoantistoffen in bijna alle UA patiënten afwezig waren, waren er geen verschillen in percentages remissie, medicatie vrije remissie en radiologische schade progressie na 1 jaar (*hoofdstukken 3 en 4*). Naast het feit dat de 'window of opportunity' in de meeste patiënten wellicht gemist is, kunnen sommige UA patiënten ook andere reumatische aandoeningen hebben gehad die niet op de gegeven therapie reageerden.

ANTISTOFFEN TEGEN GECITRULLINEERDE EIWITTEN

De aanwezigheid van ACPA in patiënten met RA is geassocieerd met een hogere ziekteactiviteit, meer beperkingen in het dagelijks functioneren en meer gewrichtsschade. Daarom is het verrassend dat patiënten met en zonder aanwezigheid van ACPA even frequent remissie en medicatie vrije remissie na 1 jaar bereikten (*hoofdstuk 6*). Ook waren er geen verschillen in dagelijks functioneren en radiologische schade progressie. Na 4 maanden behandeling met MTX en prednison bereikten ACPA positieve patiënten zelfs vaker remissie dan ACPA negatieve patiënten (*hoofdstuk 3*). Dit zou kunnen betekenen dat ACPA positieve patiënten meer baat hebben bij deze behandeling. Eerder hebben resultaten van de PROMPT studie het gunstige effect van MTX monotherapie ten opzichte van placebo aangetoond in ACPA posi-

tieve UA patiënten. Alleen in ACPA positieve patiënten werd de progressie naar RA uitgesteld en radiologische schade progressie onderdrukt. Dit zou kunnen betekenen dat verschillende pathologische mechanismen ten grondslag liggen aan de gewrichtsontstekingen in ACPA positieve en negatieve patiënten.

Van de patiënten die na 4 maanden remissie bereikten, en volgens het protocol na een jaar medicatie vrije remissie konden bereiken, bereikten 32% dit ook daadwerkelijk (*hoofdstuk 6*). Hiervan was 55% ACPA positief, vergeleken met 61% van de patiënten in vroege remissie die geen medicatie vrije remissie bereikten na 1 jaar (geen significant verschil). Wel waren patiënten die medicatie vrije remissie na 1 jaar bereikten minder vaak RF positief (50% versus 62%). In de 4 maanden na het bereiken van medicatie vrije remissie, verloren 30% van de patiënten (medicatie vrije) remissie. Deze patiënten waren vaker ACPA positief dan patiënten die medicatie vrije remissie behielden (72% versus 47%), en ACPA positieve patiënten waren minder vaak in staat medicatie vrije remissie 4 maanden te behouden dan ACPA negatieve patiënten (58% versus 80%). Deze resultaten kunnen betekenen dat, met de huidige behandelstrategie, ACPA positieve en negatieve patiënten even frequent remissie bereiken en tijdens het afbouwen van medicatie remissie even goed behouden, maar dat ACPA positieve patiënten medicatie vrije remissie minder goed behouden dan ACPA negatieve patiënten.

METACARPAAL BMD VERLIES ALS VOORSPELLER VAN RADIOLOGISCHE SCHADE

Het voorspellen van de ernst van het ziektebeloop van patiënten met RA kan de keuze van behandeling beïnvloeden. Hiermee kan zowel overbehandeling, met onnodige bijwerkingen als gevolg, als onderbehandeling met onnodige gewrichtsschade als gevolg, voorkomen worden. Het is tegenwoordig echter nog niet mogelijk om bij alle patiënten een nauwkeurige voorspelling van het ziektebeloop te geven. Daarom is er vraag naar nieuwe voorpellers van ziektebeloop die al in een vroege fase aanwezig zijn.

De mate van metacarpaal BMD verlies tijdens de eerste 4 maanden van de IMPROVED studie was voorspellend voor radiologische schade progressie na 1 jaar (*hoofdstuk 8*). Radiologische schade progressie na 1 jaar was aanwezig in 28 (7%) patiënten van de onderzochte subgroep uit de IMPROVED studie. Patiënten met radiologische progressie na 1 jaar hadden vaker metacarpaal BMD verlies in de eerste 4 maanden dan patiënten zonder schade progressie na 1 jaar (86 versus 53%). Naast metacarpaal BMD verlies tijdens de eerste 4 maanden was ook de aanwezigheid van erosies bij aanvang van de studie voorspellend voor gewrichtsschade. In 86% van de patiënten waren echter geen erosies bij aanvang van de studie aanwezig, terwijl 17 van deze patiënten na 1 jaar wel radiologische schade progressie bleken te hebben (63% van de 28 patiënten met schade progressie na 1 jaar). In deze patiënten is metacarpaal BMD verlies na 4 maanden de enige voorspeller voor schade.

Bij voorkeur is een voorspeller zo vroeg mogelijk in het ziektebeloop aanwezig, het liefst reeds op het moment dat de diagnose wordt gesteld. Voorheen bekende voorspellers, zoals de aanwezigheid van ACPA, RF en een verhoogde bezinking of C-reactive protein (CRP), bleken in deze populatie met vroege artritis echter niet voorspellend te zijn voor toekomstige schade, evenmin als het behalen van remissie na 4 maanden. Dit kan worden verklaard doordat radiologische schade goed onderdrukt werd door de huidige behandelstrategie of doordat in deze vroege populatie überhaupt nog weinig schade progressie aanwezig was. Dus ondanks het feit dat metacarpaal BMD verlies pas na 4 maanden wordt bepaald, kan het in de klinische praktijk een toegevoegde waarde hebben in het voorspellen van gewrichtsschade in patiënten met vroege RA. Toevoeging van deze voorspeller aan bestaande predictie modellen zou deze kunnen verbeteren, met als doel om in de toekomst beslissingen ten aanzien van behandeling vroeg in het ziektebeloop te kunnen sturen.

TOEKOMSTPERSPECTIEVEN

De resultaten in dit proefschrift suggereren dat met de huidige behandelstrategie ziekteuitkomsten daadwerkelijk zijn verbeterd in een vroege fase van RA. Meer patiënten bereikten remissie en medicatie vrije remissie vroeger in het ziektebeloop dan ooit te voren en radiologische schade progressie deed zich nauwelijks voor. Toekomstige resultaten van de IMPROVED studie geven antwoord op de vragen of en hoe lang medicatie vrije remissie kan worden behouden, of medicatie vrije remissie ook kan worden bereikt in patiënten die geen vroege remissie behaalden, of radiologische schade progressie ook na een langere periode nagenoeg afwezig blijft en wat de beste vervolg behandeling is voor patiënten die geen remissie bereikten na 1 jaar.

Na het eerste studie jaar bereikten ruim de helft van de patiënten remissie, en ruim 20% was zelfs in medicatie vrije remissie. Om deze uitkomsten in het merendeel, of zelfs in alle patiënten te bereiken, behoeven de huidige behandelstrategieën verdere optimalisatie. Toekomstig onderzoek zal moeten uitwijzen wat het optimale tijdstip is om te starten met behandeling. Wellicht bevindt dit tijdstip zich al binnen twaalf weken na aanvang van symptomen. Zo vroeg starten met behandeling brengt echter het risico van overbehandeling met zich mee. Afbouwen van medicatie zodra remissie is bereikt kan het risico op schade door overbehandeling zo veel mogelijk reduceren.

Over het algemeen wordt aangenomen dat remissie als behandeldoel leidt tot betere uitkomsten dan lage ziekteactiviteit als behandeldoel, wat lijkt te worden te onderschreven door de resultaten in dit proefschrift. Er is echter nooit een gerandomiseerde studie gedaan waarin streven naar beide doelen met elkaar is vergeleken. Totdat een dergelijk onderzoek is gedaan kan een definitieve uitspraak over eventuele voordelen van sturen op remissie ten opzichte van sturen op lage ziekteactiviteit, dus niet worden gedaan.

Het tijdelijk toevoegen van prednison aan behandeling met een of meerdere DMARDs kan de nieuwe hoeksteen worden van de behandeling van RA. Eerder onderzoek heeft laten zien dat combinatie behandeling met prednison even effectief is als combinatie behandeling met een biological, maar prednison is een veel goedkoper alternatief met wellicht een lagere kans op bijwerkingen. De optimale dosering en duur van de prednison behandeling is echter nog niet vastgesteld. Ook zal toekomstig onderzoek uitvoeriger moeten bevestigen dat de lange termijn bijwerkingen van kortdurende behandeling met lage dosering prednison waarschijnlijk verwaarloosbaar zijn.

De huidige resultaten suggereren dat patiënten die geen remissie bereiken na de initiële behandeling met MTX en prednison, frequenter remissie bereiken wanneer vervolg behandeling met adalimumab direct wordt gestart dan wanneer adalimumab pas wordt gestart na falen op een uitbreiding van DMARDs. Of ook medicatie vrije remissie frequenter wordt bereikt en radiologische schade progressie minder frequent optreed, moet nog worden bezien. Mocht dit het geval zijn, dan zou combinatie behandeling met adalimumab de optimale vervolg stap zijn in patiënten die geen remissie bereiken na initiële behandeling met MTX en prednison.

Om het ziekte beloop van zoveel mogelijk patiënten adequaat te kunnen voorspellen, gaat de zoektocht naar nieuwe voorspellers van ziekte-uitkomsten onverminderd door. Metacarpaal BMD verlies kan bijdragen aan een betere voorspelling van het ziekte beloop en hierdoor ook aan het vinden van de best passende behandeling voor iedere individuele patiënt.

Concluderend suggereren de resultaten in dit proefschrift dat de huidige behandelstrategie, waarin combinatie behandeling vroeg in het ziektebeloop wordt gestart en behandeling gestuurd wordt op remissie, heeft bijgedragen aan de hoge percentages remissie en medicatie vrije remissie en het nagenoeg afwezig zijn van radiologische schade na 1 jaar in patiënten met vroege (reumatoïde) artritis. Er blijft echter ruimte voor verbetering van de huidige behandelstrategieën, met als ultiem doel om deze uitkomsten in de toekomst te bereiken in iedere patiënt met reumatoïde artritis.

Appendix

CURRICULUM VITAE

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Geboren	1979	22 december, Roermond
Lagere school	1984-1992	Basisschool't Kempke, St. Odiliënberg, Limburg
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Opleiding tot reumatoloog	2013-2016	Leids Universitair Medisch Centrum, Leiden

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