TREATMENT OF EARLY RHEUMATOID AND UNDIFFERENTIATED ARTHRITIS

Lotte Heimans

ISBN: 978-94-6182-429-5

The research presented in this thesis was performed at the department of Rheumatology at the Leiden University Medical Center, Leiden. The research was financially supported by AbbVie, the Dutch Arthritis Foundation, the Netherlands Organisation for Scientific Research, the Dutch College for Health Insurances, Janssen Biologics B.V. and Schering-Plough B.V.

Cover photograph: Poppy, 1988 © The Robert Mapplethorpe Foundation. Used by permission.

Layout and printing: Off Page (www.offpage.nl)

The publication of this thesis was financially supported by the Dutch Arthritis Foundation (Reumafonds), AbbVie B.V., Pfizer B.V., Roche B.V. and UCB Pharma B.V.

TREATMENT OF EARLY RHEUMATOID AND UNDIFFERENTIATED ARTHRITIS

Proefschrift

ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
op gezag van Rector Magnificus prof.mr. C.J.J.M. Stolker,
volgens besluit van het College voor Promoties
te verdedigen op dinsdag 13 mei 2014
klokke 11:15 uur

door

Lotte Heimans

geboren te Amsterdam
in 1985

PROMOTIECOMMISSIE

Promotor:	prof. dr. T.W.J. Huizinga
Co-promotor:	dr. C.F. Allaart
Overige leden:	prof. dr. J.W. de Fijter prof. dr. W.F. Lems (VUMC, Amsterdam) dr. E.J. Giltay

TABLE OF CONTENTS

Chapter 1	General introduction	7
Chapter 2	Five year outcomes of probable rheumatoid arthritis treated with methotrexate or placebo during the first year (the PROMPT study)	25
Chapter 3	Remission induction therapy with methotrexate and prednisone in patients with early rheumatoid and undifferentiated arthritis	37
Chapter 4	A two-step treatment strategy trial in patients with early arthritis aimed at achieving remission: the IMPROVED-study	53
Chapter 5	Outcomes of two years remission steered treatment in early arthritis patients – the IMPROVED-study	67
Chapter 6	Determinants of drug free remission in patients with early rheumatoid or undifferentiated arthritis after one year of remission steered treatment	81
Chapter 7	Association of high body mass index with decreased treatment response to combination therapy in recent–onset rheumatoid arthritis patients	91
Chapter 8	Can we prevent Rapid Radiological Progression in patients with early arthritis?	105
Chapter 9	Four-month metacarpal bone mineral density loss predicts radiological joint damage progression after 1 year in patients with early rheumatoid arthritis – exploratory analyses from the IMPROVED-study	113
Chapter 10	The relationship between disease activity and depressive symptoms severity and optimism – results from the IMPROVED-study	127
Chapter 11	Health related quality of life and functional ability in patients with early arthritis during remission steered treatment – results of the IMPROVED-study	139
Chapter 12	Summary and conclusion	155
Chapter 13	Nederlandse samenvatting	173
Appendix	Role of the funding source	191
	List of publications	193
	Curriculum vitae	195
	Dankwoord	197

CHAPTER 1

GENERAL INTRODUCTION

This thesis describes the outcomes of different treatment strategies in patients with early arthritis and is, for a large part, based on results of the IMPROVED-study (Induction therapy with Methotrexate and Prednisone in Rheumatoid Or Very Early arthritic Disease). First a general overview is given, starting with the clinical picture of rheumatoid and undifferentiated arthritis as known to date, followed by an introduction on currently available therapies and possible treatment strategies. Then an overview of the various outcome measures which are referred to in the thesis, followed by a short discourse on the concept of treatment response and the prediction of that response. In the last section, the IMPROVED-study is explained in more detail.

RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a systemic auto-immune disease characterized by inflammatory arthritis.[1] RA affects approximately 0.5-1% of the population worldwide and women are affected two to three times more often than men.[2] The exact aetiology of RA is still unknown, but it appears that several genes and environmental factors act together to cause the disease.[1]

Patients with RA can present with systemic symptoms such as fatigue, fever, malaise and weight loss and usually have complaints of morning stiffness and symptoms of joint swelling and pain of mainly the small joints of the hands and feet and often other peripheral joints.[3] These symptoms cause impairments in functional capacity which frequently leads to a decreased work ability and restrictions in social activities and quality of life.[4, 5] In early stages of RA, functional capacity is most impaired by disease activity (inflammation) while later in the disease course damage that has occurred in affected joints contributes to functional impairment which is then irreversible even with effective antirheumatic drugs.[6]

The diagnosis of rheumatoid arthritis is based on patient assessment by a trained physician. To facilitate identification of patients with RA in clinical trials and scientific publications, classification criteria were formulated. In the 1950s, the first classification criteria for RA were published by the American College of Rheumatology (ACR),[7] which were revised in 1987.[8] With a growing awareness among rheumatologists that patients with RA need to start treatment as early as possible, it was felt that the old criteria were inadequate to identify patients in the earliest stages of the disease. Therefore, new classification criteria were published by the ACR and the European League Against Rheumatism (EULAR) in 2010. These criteria allow classification of patients with arthritis of a short duration with clinical and/or laboratory features known to be associated with a risk of persistence of symptoms and/or structural joint damage. Classification of these patients as having RA should enable earlier treatment initiation, also in clinical trials (table 1).[9]

Table 1. The 2010 American College of Rheumatology/European League against Rheumatism classification criteria for rheumatoid arthritis.[9]

Target population: patients who have at least 1 joint with definite clinical synovitis (swelling) with the synovitis not better explained by another disease. A score of ≥6/10 is needed for classification of a patient as having definite RA.	
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
Abnormal CRP or abnormal ESR	1
Duration of symptoms:	
< 6 weeks	0
≥ 6 weeks	1

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

UNDIFFERENTIATED ARTHRITIS

Undifferentiated arthritis (UA) is a term commonly used for inflammatory arthritis where a specific rheumatic disease could not be diagnosed. There is an overlap with what was called 'probable rheumatoid arthritis' and 'possible rheumatoid arthritis', for which the ACR provided classification criteria in the 1950s.[7] Several databases have included patients with UA to determine how symptoms, laboratory features and radiological outcomes might develop over time. The results, in part, depend on the initial definition of UA and the inclusion criteria.[10]

Spontaneous remission has been reported in 40-55% of UA patients and progression to RA in 17-32%.[10, 11] Thus, in a subset of patients UA can be considered to be an early stage of RA. Radiographic progression, disease activity and functional capacity have shown to be similar in patients who present with UA but progress to RA in 1 year as in patients who present directly with classifiable early RA.[12] Although several models have been developed to identify which UA patient has 'very early RA', it remains a challenge to predict progression, or alternatively spontaneous remission, in each individual UA patient correctly. This means that a decision to start antirheumatic treatment still largely depends on the physician's insight or 'gut feeling'.

ANTIRHEUMATIC TREATMENT

Non-biologic Disease-modifying antirheumatic drugs

Non-biologic disease-modifying antirheumatic drugs (DMARDs) are still the initial treatment in most patients with RA and are sometimes also used in patients with UA. Methotrexate (MTX) is considered the 'anchor drug' in RA since it has proven to be effective with acceptable toxicity.[13] Other synthetic DMARDs often used in the treatment of RA are sulphasalazine[14] (SSZ), leflunomide[15] and the moderately effective antimalarial hydroxychloroquine (HCQ).[16, 17] DMARDs are often used in combination with other non-biologic DMARDs, but also with (low dose) corticosteroids or biologic DMARDs (see below). In 1996 O'Dell and colleagues presented the 'O'Dell scheme' in patients with advanced RA who failed on previous DMARD monotherapy. O'Dell's combination of MTX, SSZ and HCQ, proved to be superior to either MTX alone or combinations of SSZ plus HCQ, MTX plus SSZ, or MTX plus HCQ.[18] Recently, the combination of MTX with SSZ and HCQ was shown to be no less effective than MTX with etanercept, a biologic DMARD, in patients with RA who had insufficient response on MTX alone[19] and more effective than MTX monotherapy in patients with UA with a high risk of RA.[20]

Corticosteroids

Parenteral and oral corticosteroids are often used in the treatment of RA, usually in combination with DMARDs. Steroids suppress inflammation leading to rapid improvement of clinical parameters and, as shown for oral corticosteroids and possibly also intra-articular corticosteroid injections, to a reduction in erosive joint damage.[21-24] Despite its benefits, doctors and patients often have concerns about the potential side effects of oral corticosteroids such as the Cushing face, osteoporosis, myopathy, glucose intolerance or cardiovascular disease.[25, 26] It is therefore recommended to use oral corticosteroids in low doses and discontinue as soon as possible.[27]

Biologic DMARDs

Tumour Necrosis Factor (TNF) alpha, a cytokine produced by monocytes, macrophages and lymphocytes, stimulates and induces inflammation. It is found in the synovial fluid in the joints of patients with RA and is associated with synovitis and joint destruction.[28, 29] TNF-alpha inhibitors, most often in combination with methotrexate, have shown to be effective anti-rheumatic drugs, suppressing symptoms as well as radiological joint damage progression in the majority of patients.[30, 31]

Currently, there are five TNF-alpha inhibitors available for treatment of RA; infliximab (IFX), adalimumab (ADA), certolizumab, golimumab and etanercept. Current rules on reimbursement of the costs of these expensive drugs require that RA patients have had previous treatment with MTX and at least one other non-biologic DMARD but still have active disease. Other biologic DMARDs have also become available for patients with active RA (despite treatment with non-biologic DMARDs and TNF-alpha inhibitors):

toculizumab (anti-IL-6), abatacept (a T-cell costimulation inhibitor) and rituximab (a B-cell depletor). These drugs do not feature in this thesis and are no further discussed.

TREATMENT STRATEGIES

During the last decades, much has changed in the treatment of patients with arthritis with the aim to improve disease outcomes.[32, 33] Until the 1980s, patients with RA were treated according to the 'pyramid strategy', first with either aspirin or other non-steroidal anti-inflammatory drugs (NSAID). Only if joint damage occurred DMARDs were started, which were thought to be so potentially harmful that the way to use them was 'go low, go slow'.[34] Any improvement in clinical symptoms was considered a good response. When it became clear that DMARD toxicity was not significantly worse than NSAID toxicity, DMARDs were started earlier in the disease course and there were more treatment adjustments when the clinical response was insufficient.[32, 35, 36] This so-called 'sawtooth strategy' was superior to the 'pyramid strategy'; more patients had adequate suppression of symptoms and also joint damage was better suppressed.[37, 38]

After multiple decades of research, changing treatment paradigms, resulting in ever improving disease outcomes, there are a few concepts dominating the current treatment approaches in RA. The first concept is that treatment should be initiated directly after diagnosis.[39, 40] This was one of the reasons why the classification criteria for RA were again revised in 2010, to be able to identify patients with early RA. Rheumatologists are recommended to start treatment in patients with any arthritis that is likely to progress, become chronic or lead to structural damage.[9, 41] Second, many trials have shown that initial combination therapy, especially when including prednisone or a TNF-alpha inhibitor, leads to a better suppression of disease activity, better functional ability and less radiological damage progression without the burden of increased toxicity, when compared to monotherapy.[18, 20, 21, 31, 42-44] This notwithstanding the fact that MTX monotherapy may be effective in a selection of patients, although it may take more time to achieve than with the aforementioned combinations of drugs.[45, 46] Since it is not reliably possible to identify which patients would benefit from methotrexate alone, starting with a combination treatment in all patients allows more rapid response and avoids undertreatment. The third concept is that disease activity should be monitored frequently ('tight control') and that treatment should be adjusted in order to achieve and maintain a predefined target level of disease activity (for instance a threshold of a composite score that represents signs and symptoms of inflammation). This is called the 'treat to target' approach.[22, 47]

The same principles are advocated for those patients with UA which is considered an early phase of RA. Initiation of treatment already in the phase of UA might possibly induce permanent remission or at least stop the disease process and prevent progression to RA. This early and restricted period of time in which alteration of the disease course might be possible, is often called the window-of-opportunity.[48]

How to treat UA remains undecided. In the PROMPT study it was shown that one year of MTX monotherapy only postponed but did not prevent progression to RA.[49] It might be possible that initial combination therapy with prednisone or early use of a TNF-alpha inhibitor in UA will prevent progression to RA and induce remission without joint damage and with restored functional ability.

DISEASE OUTCOMES

Disease Activity Score (DAS)

The Disease Activity Score (DAS) is one of the composite measures to assess disease activity in patients with arthritis. It may be used in clinical trials to compare treatment response and in daily practice to register disease activity over time and to measure the response to treatment, intensifying treatment until the treatment target is achieved and tapering when disease activity is persistently low.

The DAS combines the results of four components; the number of painful joints represented in a tender joint count which is called the Ritchie Articular Index (RAI)[50], the number of swollen joints (the swollen joint count), global health as indicated by the patient on a 100 mm visual analogue scale (VAS) and the erythrocyte sedimentation rate (ESR). The DAS is calculated according to the following formula: $0.54\sqrt{(RAI)} + 0.065(\text{swollen joint count}) + 0.33\ln(ESR) + 0.0072VASgh$. The DAS is based on evaluation of 44 joints for joint swelling and 53 joints for joint tenderness, compared to the DAS28 which is based on examination of only 28 joints.[51]

Remission

Remission has become a realistic goal for many patients.[52] According to the European League Against Rheumatism (EULAR) recommendations for the management of rheumatoid arthritis (2010), remission is the primary aim of treatment, especially in patients with early RA.[27] The FIN-RACo trial was one of the first trials aiming for remission as a treatment goal.[44] After 11 years follow-up they concluded that treatment targeted at remission has long term benefits when it comes to disease outcomes and that it greatly suppresses radiological joint damage progression.[53]

Various definitions of remission are used and in general it can be defined as the absence of (troublesome) disease activity.[54] The FIN-RACo trial used the old ACR remission criteria (≥ 5 of the following, for at least 2 consecutive months: morning stiffness <15 minutes, no fatigue, no joint pain, no joint tenderness or pain on motion, no soft tissue swelling in joints or tendon sheaths and an ESR <30 mm/hour for a female or <20 mm/hour for a male)[55] leaving out the absence of fatigue. A DAS <1.6 was found to be equivalent to absence of disease as represented by those ACR remission criteria.[56] In 2011, a collaboration of the ACR, the EULAR and the Outcome Measures in Rheumatology (OMERACT) initiative resulted in a definition of remission in RA based on composite measures of disease activity (using the simplified disease activity index score (SDAI) which should be <3.3)) or using a Boolean approach, which describes a patient to be in remission when he or she

has a tender joint count ≤1, a swollen joint count ≤1, a C-reactive protein (CRP) ≤1mg/dl and a patient global VAS-score ≤1 (on a scale of 0-10 centimeter).[57]

Ideally, after early and effective treatment, patients continue to be in remission while medication is tapered and finally stopped, to achieve drug free remission (DFR). In daily practice this is sometimes achieved and in one clinical trial (the BeSt study) aiming for DFR was integrated in the treatment protocol.[45] In a previous evaluation of the predictors of DFR, it was found that a symptom duration less than 12 weeks and absence of anti-citrullinated protein antibodies (ACPA) increased the chance of sustained DFR. There was no clear association between a targeted treatment strategy (aiming at low disease activity) and achieving DFR in that study.[58]

Functional ability

Functional ability is one of the most reported outcome measures in clinical practice and in clinical trials. In the Netherlands it is measured with the Dutch version of the Health Assessment Questionnaire (HAQ).[35, 59] The HAQ is a 24-item questionnaire to assess the level of difficulty the patient is having with activities of daily living. These activities are divided into eight categories; dressing, rising, eating, walking, personal hygiene, reach, grip and errands. Per question the score ranges between 0 (no difficulties doing this) and 3 (unable to do this). By summing the highest score within each category and dividing it by 8, the total score ranges from 0 to 3. The minimum clinically important difference is 0.22.[60]

In addition to the HAQ, the McMaster-Toronto Arthritis Patients Preference Questionnaire (MACTAR) also measures functional ability. Patients have to rank a maximum of five activities in which they are experiencing problems as a result of their arthritis. Over time, improvement or deterioration of these five activities can be monitored. The change scores from baseline vary between -38 (maximum deterioration) to +38 (maximum improvement). The MACTAR is sensitive to change and useful to detect small differences.[61, 62]

Quality of life and psychological well being

Treatment to suppress disease activity may lead to symptom relief and this may result in improvement of patient reported outcomes (PROs) such as health related quality of life (HRQoL) and mental wellbeing.[63]

HRQoL can be assessed using the Short-Form 36 (SF-36). This widely used questionnaire measures eight domains of health; physical functioning, role limitations due to physical and due to emotional functioning, bodily pain, general health, vitality, social functioning and mental health. The total score ranges from 0 (worst) to 100 (best). Based on the scores in the different domains, a mental component score (MCS) and a physical component score (PCS) can be calculated. These component scores are standardized, based on the worldwide population norm, to a mean of 50 and a standard deviation of 10.[64, 65] The minimum clinically important difference is a 5-10 point difference from baseline for the subscales and 2.5-5 points for the component scores.[66]

Depressive symptoms are more common in patients with RA, compared to healthy individuals.[67-70] The association between depression and arthritis may be explained by decreased functioning and pain, but may also be an effect of inflammatory processes.[71, 72] Therefore, suppression of disease activity and especially achieving clinical remission may improve depressive symptoms.[67] Depressive symptoms severity can be measured with the Beck Depression Inventory II (BDI-II). Based on the diagnostic criteria for major depression as described in the DSM-IV, a sum of scores is composed ranging from 0-63. A total score of 0-13 indicates minimal depressive symptoms, a score of 14-19 denotes mild depressive symptoms, 20-28 moderate depressive symptoms and 29-63 severe depressive symptoms.[73] Another focus on mood is optimism, a trait which can be assessed with the 10-item Life Orientation Test Revised (LOT-R). The total score ranges between 0 and 24 and a higher score means a person is more optimistic.[74] Low dispositional optimism has been defined as a total score <12.[75]

Radiological joint damage

Radiological joint damage can be assessed on radiographs of the hands, wrists and feet with the modified Sharp-van der Heijde score (SHS). The proximal interphalangeal (PIP) and metacarpophalangeal (MCP) joints of the hands, six areas in each wrist, the metatarsophalangeal (MTP) and both hallux interphalangeal joints of the feet are scored for erosions and joint space narrowing. The maximum score is 448.[76]

Progression of joint damage over time is often used as an outcome measure in clinical trials. Rapid Radiological Progression (RRP) is defined as an increase in SHS of ≥5 points in the first year after diagnosis and is associated with more severe damage progression in a later phase of the disease.[77-79] Risk factors for rapid progression of joint damage may help guiding clinicians in their choice for the initial treatment step which may help to prevent RRP. In the BeSt study a matrix model to assess the risk of RRP was developed in patients with recent onset active RA. The model predicts the risk of RRP based on status for rheumatoid factor (RF) and/or ACPA, CRP, the number of erosions at baseline and initial treatment choice (either initial MTX monotherapy or initial combination therapy of MTX with SSZ and prednisone or with IFX).[80]

As patients are treated in more early disease stages and according to treat-to-target strategies aiming at remission, fewer patients show radiological joint damage progression and damage is generally less severe.[6, 47] Because of that, it may become difficult to compare the effect of various therapies on inhibition of structural joint damage.[81] For individual patients radiological damage progression as treatment outcome may become increasingly irrelevant compared to symptoms of inflammation since the changes found on radiographs are too limited to have impact on, for instance, functional ability. Evaluating the effect of treatment on cartilage and bone is still scientifically relevant and may require other imaging techniques and/or serum biomarker studies where plain radiographs are inept to measure subtle changes and provide insufficient information.[82]

Bone mineral density measurement

Metacarpal osteopenia is a very early manifestation of RA not detected by conventional radiographs.[83, 84] Subtle changes in metacarpal bone mineral density (mBMD) can be measured with Digital X ray Radiogrammetry (DXR). In patients with early RA, mBMD loss during the first year after diagnosis is predictive for radiological damage up to five years afterwards. mBMD loss is associated with persistent disease activity and mBMD gain is seen in patients in prolonged clinical remission.[85-88] It may be possible that early mBMD loss, measured in the first few months of treatment, may represent a risk factor for joint damage progression already after 1 year. If so, very early mBMD loss may trigger early treatment adjustments in RA.

RESPONSE TO TREATMENT

Individualized treatment would help to avoid both lack of response and delay in improvement with the risk of damage progression (undertreatment) as well as the risk of potential side effects and in some cases high costs of therapies which in retrospect would have been unnecessary (overtreatment). Individualized treatment would be possible if we could predict the response to treatment.[89-92]

Multiple predictors of response to treatment have been identified, mainly disease characteristics at baseline; disease activity, functional ability, radiological joint damage, acute phase reactants and the presence of autoantibodies like ACPA and RF.[89, 91, 93] It appears that also body mass index (BMI) may be associated with treatment response, as it was reported that patients with a high BMI responded less well to combination therapy with MTX and IFX, than patients with low or normal BMI.[94]

THE IMPROVED-STUDY

The IMPROVED-study (Induction therapy with Methotrexate and Prednisone in Rheumatoid Or Very Early arthritic Disease) is a multicentre, single-blind, randomized clinical trial in patients with recent-onset arthritis. In 12 centers in the Western part of the Netherlands, over 600 patients with UA and early RA were included between May 2007 and September 2010. RA was defined according to the 2010 ACR/EULAR classification criteria[9] with a symptom duration of ≤2 years. Patients were classified as UA if they had at least one joint with synovitis and one other painful joint which was clinically suspected for early RA, regardless of symptom duration.

In patients with UA in the PROMPT-study it was shown that MTX monotherapy only postponed and not prevented progression to RA.[49] In clinical trials in patients with RA, initial combination therapy including methotrexate and prednisone resulted in earlier improvement and better outcomes than monotherapy with non-biologic DMARDs.[20, 21, 42, 95, 96] The IMPROVED-study was designed to start with such a combination both in very early RA and UA to see whether it was possible to induce remission and DFR and stop damage progression. Thus, all patients

in the IMPROVED-study were initially treated with a combination of MTX (25mg/week) and a tapered high dose of prednisone (started at 60mg/day for one week and then tapered to 7,5 mg/day in 7 weeks) during the first 4 months.

The BeSt-study and the TICORA-trial have shown that a tight controlled treatment strategy targeted at low disease activity or remission leads to better disease outcomes.[42,47] Up to 48% of the patients in the BeSt study achieved a DAS<1.6, while treatment was steered at a DAS≤2.4, and up to 14% achieved DFR.[45] To try to improve these results, the IMPROVED treatment strategy is remission steered, with remission defined as a DAS<1.6 ('DAS-remission').[56] Every four months a DAS-evaluation was performed and based on the DAS, treatment was adjusted (figure 1).

If DAS-remission was achieved, medication was tapered and or stopped. In case DAS-remission was not achieved, medication was intensified (with a dose increase, drug switch or restart of medication that was previously discontinued). Patients who did not achieve DAS-remission after 4 months of initial combination therapy were randomized into 2 treatment strategy arms to answer which approach would result in more (drug free) remission. In arm 1, a combination of MTX, SSZ, HCQ and low dose prednisone was used, if that failed to induce DAS-remission adalimumab with MTX was started. In arm 2, adalimumab with MTX was started immediately. In both arms, adalimumab

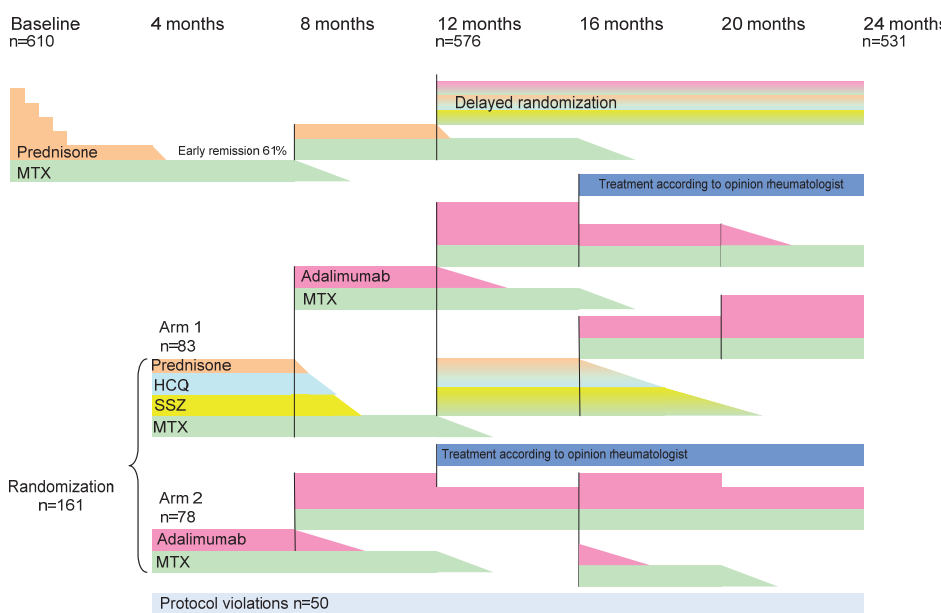

Figure 1. Study flow chart up until the second study year. MTX: methotrexate, HCQ: hydroxychloroquine, SSZ: sulfasalazine. Colours: orange=prednisone, green=MTX, dark blue=treatment left to decision of rheumatologist, aqua=HCQ, yellow=SSZ, purple=adalimumab biweekly, double thickness purple=adalimumab weekly, grey=protocol not followed as required but remained in follow up.

was to be increased (from 40 mg every 2 weeks to 40 mg weekly) if DAS-remission was not achieved. If DAS-remission was still not achieved on 40 mg weekly, the next choice of treatment was left to the decision of the treating physician, with DAS-remission as treatment target and the intention to taper and ultimately stop medication. The IMPROVED treatment strategy is visualized in figure 1.

Radiological damage progression, mBMD changes, functional ability, quality of life and depressive symptoms severity were to be measured over time and compared in relation to remission rates and between patients with UA and RA and between patients with and without ACPA.

OUTLINE OF THIS THESIS

It remains a challenge to further optimize and improve treatment and treatment outcomes for patients with early (rheumatoid) arthritis. This thesis focuses on various treatment strategies as well as predictors for response to treatment and different kinds of outcome measures, varying from remission and joint damage progression to psychological wellbeing.

Chapter 2 describes disease outcomes in patients with undifferentiated arthritis (UA) 5 years after initial treatment with methotrexate (MTX) or placebo in the PROMPT study. In **chapter 3** the main outcomes together with predictors for early remission after the first four months of remission steered treatment in the IMPROVED-study are evaluated. In **chapter 4 and chapter 5** the outcomes after respectively one and two years follow-up in the IMPROVED-study are described. In **chapter 6** the influence of baseline characteristics on the possibility to achieve drug free remission (DFR), is investigated. In **chapter 7** the association between high body mass index (BMI) and treatment response in patients with recent onset rheumatoid arthritis (RA) in the BeSt study is assessed. **Chapter 9** describes the performance of a matrix model to predict damage progression designed in the BeSt study and asks the question whether rapid radiological progression (RRP) still exists. In the last two chapters the associations between various patient reported outcomes (PROs) and disease activity and remission in the IMPROVED-study are described. **Chapter 10** describes the severity of depressive symptoms and dispositional optimism both before and after the first four months of therapy. Follow-up of functional ability and health related quality of life (HRQoL) during the first study year and the association with remission are described in **chapter 11**.

REFERENCE LIST

1. Klareskog L, Catrina AI, Paget S. Rheumatoid arthritis. Lancet 2009;373(9664):659-672.
2. Alamanos Y, Voulgari PV, Drosos AA. Incidence and prevalence of rheumatoid arthritis, based on the 1987 American College of Rheumatology criteria: a systematic review. Semin Arthritis Rheum 2006;36(3):182-188.
3. Grassi W, de Angelis R, Lamanna G, Cervini C. The clinical features of rheumatoid arthritis. Eur J Radiol 1998;27 Suppl 1:S18-S24.

4. Neovius M, Simard JF, Klareskog L, Askling J. Sick leave and disability pension before and after initiation of antirheumatic therapies in clinical practice. Ann Rheum Dis 2011;70(8):1407-1414.
5. Lubeck DP. Patient-reported outcomes and their role in the assessment of rheumatoid arthritis. Pharmacoeconomics 2004;22(2 Suppl 1):27-38.
6. Welsing PM, van Gestel AM, Swinkels HL, Kiemeney LA, van Riel PL. The relationship between disease activity, joint destruction, and functional capacity over the course of rheumatoid arthritis. Arthritis Rheum 2001;44(9):2009-2017.
7. Ropes MW, Bennett GA, Cobb S, Jacox R, Jessar RA. 1958 Revision of diagnostic criteria for rheumatoid arthritis. Bull Rheum Dis 1958;9(4):175-176.
8. Arnett FC, Edworthy SM, Bloch DA et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31(3):315-324.
9. Aletaha D, Neogi T, Silman AJ et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/ European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010;69(9):1580-1588.
10. Verpoort KN, van Dongen H, Allaart CF, Toes RE, Breedveld FC, Huizinga TW. Undifferentiated arthritis--disease course assessed in several inception cohorts. Clin Exp Rheumatol 2004;22(5 Suppl 35):S12-S17.
11. Harrison BJ, Symmons DP, Brennan P, Barrett EM, Silman AJ. Natural remission in inflammatory polyarthritis: issues of definition and prediction. Br J Rheumatol 1996;35(11):1096-1100.
12. van Aken J, van Dongen H, le Cessie S, Allaart CF, Breedveld FC, Huizinga TW. Comparison of long term outcome of patients with rheumatoid arthritis presenting with undifferentiated arthritis or with rheumatoid arthritis: an observational cohort study. Ann Rheum Dis 2006;65(1):20-25.
13. Pincus T, Yazici Y, Sokka T, Aletaha D, Smolen JS. Methotrexate as the "anchor drug" for the treatment of early rheumatoid arthritis. Clin Exp Rheumatol 2003;21(5 Suppl 31):S179-S185.
14. Hannonen P, Mottonen T, Hakola M, Oka M. Sulfasalazine in early rheumatoid arthritis. A 48-week double-blind, prospective, placebo-controlled study. Arthritis Rheum 1993;36(11):1501-1509.
15. Mladenovic V, Domljan Z, Rozman B et al. Safety and effectiveness of leflunomide in the treatment of patients with active rheumatoid arthritis. Results of a randomized, placebo-controlled, phase II study. Arthritis Rheum 1995;38(11):1595-1603.
16. Sanders M. A review of controlled clinical trials examining the effects of antimalarial compounds and gold compounds on radiographic progression in rheumatoid arthritis. J Rheumatol 2000;27(2):523-529.
17. Mittal N, Mittal R, Sharma A, Jose V, Wanchu A, Singh S. Treatment failure with disease-modifying antirheumatic drugs in rheumatoid arthritis patients. Singapore Med J 2012;53(8):532-536.
18. O'Dell JR, Haire CE, Erikson N et al. Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications. N Engl J Med 1996;334(20):1287-1291.
19. O'Dell JR, Mikuls TR, Taylor TH et al. Therapies for active rheumatoid arthritis after methotrexate failure. N Engl J Med. 2013 Jul 25;369(4):307-18.
20. de Jong PH, Hazes JM, Barendregt PJ et al. Induction therapy with a combination of DMARDs is better than methotrexate monotherapy: first results of the tREACH trial. Ann Rheum Dis 2013 Jan;72(1):72-8.
21. Boers M, Verhoeven AC, Markusse HM et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet 1997;350(9074):309-318.
22. Bakker MF, Jacobs JW, Verstappen SM, Bijlsma JW. Tight control in the treatment of rheumatoid arthritis: efficacy and feasibility. Ann Rheum Dis 2007;66 Suppl 3:56-60.
23. Kirwan JR, Bijlsma JW, Boers M, Shea BJ. Effects of glucocorticoids on radiological progression in rheumatoid arthritis. Cochrane Database Syst Rev 2007;(1):CD006356.
24. Hetland ML, Stengaard-Pedersen K, Junker P et al. Combination treatment with methotrexate, cyclosporine, and intraarticular betamethasone compared with methotrexate and intraarticular betamethasone in early active rheumatoid arthritis: an investigator-

initiated, multicenter, randomized, double-blind, parallel-group, placebo-controlled study. Arthritis Rheum 2006 May;54(5):1401-9.

25. Da Silva JA, Jacobs JW, Kirwan JR et al. Safety of low dose glucocorticoid treatment in rheumatoid arthritis: published evidence and prospective trial data. Ann Rheum Dis 2006;65(3):285-293.
26. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF et al. Patient preferences for treatment: report from a randomised comparison of treatment strategies in early rheumatoid arthritis (BeSt trial). Ann Rheum Dis 2007;66(9):1227-1232.
27. Smolen JS, Landewe R, Breedveld FC et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis 2010;69(6):964-975.
28. Christodoulou C, Choy EH. Joint inflammation and cytokine inhibition in rheumatoid arthritis. Clin Exp Med 2006;6(1):13-19.
29. Neidel J, Schulze M, Lindschau J. Association between degree of bone-erosion and synovial fluid-levels of tumor necrosis factor alpha in the knee-joints of patients with rheumatoid arthritis. Inflamm Res 1995;44(5):217-221.
30. Lipsky PE, van der Heijde DM, St Clair EW et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. N Engl J Med 2000;343(22):1594-1602.
31. Klareskog L, van der Heijde D, de Jager JP et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet 2004;363(9410):675-681.
32. Pincus T, Sokka T, Kautiainen H. Patients seen for standard rheumatoid arthritis care have significantly better articular, radiographic, laboratory, and functional status in 2000 than in 1985. Arthritis Rheum 2005;52(4):1009-1019.
33. McCarty DJ. Suppress rheumatoid inflammation early and leave the pyramid to the Egyptians. J Rheumatol 1990;17(9):1115-1118.
34. Jaffe IA. The technique of penicillamine administration in rheumatoid arthritis.
35. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23(2):137-145.
36. Fries JF. Current treatment paradigms in rheumatoid arthritis. Rheumatology (Oxford) 2000;39 Suppl 1:30-35.
37. Mottonen T, Paimela L, Ahonen J, Helve T, Hannonen P, Leirisalo-Repo M. Outcome in patients with early rheumatoid arthritis treated according to the "sawtooth" strategy. Arthritis Rheum 1996;39(6):996-1005.
38. Sokka T, Hannonen P. Utility of disease modifying antirheumatic drugs in "sawtooth" strategy. A prospective study of early rheumatoid arthritis patients up to 15 years. Ann Rheum Dis 1999;58(10):618-622.
39. Lard LR, Visser H, Speyer I et al. Early versus delayed treatment in patients with recent-onset rheumatoid arthritis: comparison of two cohorts who received different treatment strategies. Am J Med 2001;111(6):446-451.
40. Nell VP, Machold KP, Eberl G, Stamm TA, Uffmann M, Smolen JS. Benefit of very early referral and very early therapy with disease-modifying anti-rheumatic drugs in patients with early rheumatoid arthritis. Rheumatology (Oxford) 2004;43(7):906-914.
41. Cader MZ, Filer A, Hazlehurst J, de PP, Buckley CD, Raza K. Performance of the 2010 ACR/EULAR criteria for rheumatoid arthritis: comparison with 1987 ACR criteria in a very early synovitis cohort. Ann Rheum Dis 2011;70(6):949-955.
42. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. Arthritis Rheum 2005;52(11):3381-3390.
43. Breedveld FC, Weisman MH, Kavanaugh AF et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum 2006;54(1):26-37.
44. Mottonen T, Hannonen P, Leirisalo-Repo M et al. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. Lancet 1999;353(9164):1568-1573.
45. Klarenbeek NB, Guler-Yuksel M, van der Kooij SM et al. The impact of four dynamic, goal-steered treatment strategies on the

5-year outcomes of rheumatoid arthritis patients in the BeSt study. Ann Rheum Dis 2011;70(6):1039-1046.

46. Dirven L, Visser K, Klarenbeek NB et al. Towards personalized treatment: predictors of short-term HAQ response in recent-onset active rheumatoid arthritis are different from predictors of rapid radiological progression. Scand J Rheumatol 2012;41(1):15-19.
47. Grigor C, Capell H, Stirling A et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. Lancet 2004;364(9430):263-269.
48. Quinn MA, Emery P. Window of opportunity in early rheumatoid arthritis: possibility of altering the disease process with early intervention. Clin Exp Rheumatol 2003;21(5 Suppl 31):S154-S157.
49. van Dongen H, van Aken J, Lard LR et al. Efficacy of methotrexate treatment in patients with probable rheumatoid arthritis: a double-blind, randomized, placebo-controlled trial. Arthritis Rheum 2007;56(5):1424-1432.
50. Ritchie DM, Boyle JA, McInnes JM et al. Clinical studies with an articular index for the assessment of joint tenderness in patients with rheumatoid arthritis. Q J Med 1968;37(147):393-406.
51. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995 Jan;38(1):44-8.
52. Smolen JS, Aletaha D. What should be our treatment goal in rheumatoid arthritis today? Clin Exp Rheumatol 2006;24(6 Suppl 43):S-13.
53. Rantalaiho V, Korpela M, Laasonen L et al. Early combination disease-modifying antirheumatic drug therapy and tight disease control improve long-term radiologic outcome in patients with early rheumatoid arthritis: the 11-year results of the Finnish Rheumatoid Arthritis Combination Therapy trial. Arthritis Res Ther 2010;12(3):R122.
54. Felson D. Defining remission in rheumatoid arthritis. Ann Rheum Dis 2012;71 Suppl 2:i86-i88.
55. Pinals RS, Masi AT, Larsen RA. Preliminary criteria for clinical remission in rheumatoid arthritis. Arthritis Rheum 1981;24(10):1308-1315.
56. Prevoo ML, van Gestel AM, van 't Hof MA, van Rijswijk MH, van de Putte LB, van Riel PL. Remission in a prospective study of patients with rheumatoid arthritis. American Rheumatism Association preliminary remission criteria in relation to the disease activity score. Br J Rheumatol 1996;35(11):1101-1105.
57. Felson DT, Smolen JS, Wells G et al. American College of Rheumatology/European League against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Ann Rheum Dis 2011;70(3):404-413.
58. van der Woude D, Visser K, Klarenbeek NB et al. Sustained drug-free remission in rheumatoid arthritis after DAS-driven or non-DAS-driven therapy: a comparison of two cohort studies. Rheumatology (Oxford) 2012 Jun;51(6):1120-8.
59. Siegert CE, Vleming LJ, Vandenbroucke JP, Cats A. Measurement of disability in Dutch rheumatoid arthritis patients. Clin Rheumatol 1984;3(3):305-309.
60. Wells GA, Tugwell P, Kraag GR, Baker PR, Groh J, Redelmeier DA. Minimum important difference between patients with rheumatoid arthritis: the patient's perspective. J Rheumatol 1993;20(3):557-560.
61. Verhoeven AC, Boers M, van der Liden S. Validity of the MACTAR questionnaire as a functional index in a rheumatoid arthritis clinical trial. The McMaster Toronto Arthritis. J Rheumatol 2000;27(12):2801-2809.
62. Tugwell P, Bombardier C, Buchanan WW, Goldsmith CH, Grace E, Hanna B. The MACTAR Patient Preference Disability Questionnaire - an individualized functional priority approach for assessing improvement in physical disability in clinical trials in rheumatoid arthritis. J Rheumatol 1987;14(3):446-451.
63. van der Kooij SM, de Vries-Bouwstra JK, Goekoop-Ruiterman YP et al. Patient-reported outcomes in a randomized trial comparing four different treatment strategies in recent-onset rheumatoid arthritis. Arthritis Rheum 2009;61(1):4-12.
64. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30(6):473-483.
65. Aaronson NK, Muller M, Cohen PD et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol 1998;51(11):1055-1068.

66. Kosinski M, Zhao SZ, Dedhiya S, Osterhaus JT, Ware JE, Jr. Determining minimally important changes in generic and disease-specific health-related quality of life questionnaires in clinical trials of rheumatoid arthritis. Arthritis Rheum 2000;43(7):1478-1487.
67. Kekow J, Moots R, Khandker R, Melin J, Freundlich B, Singh A. Improvements in patient-reported outcomes, symptoms of depression and anxiety, and their association with clinical remission among patients with moderate-to-severe active early rheumatoid arthritis. Rheumatology (Oxford) 2011;50(2):401-409.
68. Covic T, Tyson G, Spencer D, Howe G. Depression in rheumatoid arthritis patients: demographic, clinical, and psychological predictors. J Psychosom Res 2006;60(5):469-476.
69. Pincus T, Griffith J, Pearce S, Isenberg D. Prevalence of self-reported depression in patients with rheumatoid arthritis. Br J Rheumatol 1996;35(9):879-883.
70. Dickens C, McGowan L, Clark-Carter D, Creed F. Depression in rheumatoid arthritis: a systematic review of the literature with meta-analysis. Psychosom Med 2002;64(1):52-60.
71. O'Brien SM, Scott LV, Dinan TG. Cytokines: abnormalities in major depression and implications for pharmacological treatment. Hum Psychopharmacol 2004;19(6):397-403.
72. Maes M, Bosmans E, De Jongh R, Kenis G, Vandoolaeghe E, Neels H. Increased serum IL-6 and IL-1 receptor antagonist concentrations in major depression and treatment resistant depression. Cytokine 1997;9(11):853-858.
73. Beck A. BDI-II-NL: De Nederlandse versie van de Beck depression inventory 2nd ed. 2002..
74. Scheier MF, Carver CS, Bridges MW. Distinguishing optimism from neuroticism (and trait anxiety, self-mastery, and self-esteem): a reevaluation of the Life Orientation Test. J Pers Soc Psychol 1994;67(6):1063-1078.
75. van de Rest O, de Goede J, Sytsma F et al. Association of n-3 long-chain PUFA and fish intake with depressive symptoms and low dispositional optimism in older subjects with a history of myocardial infarction. Br J Nutr 2010;103(9):1381-1387.
76. van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. J Rheumatol 2000;27(1):261-263.
77. Bruynesteyn K, van der Heijde D, Boers M et al. Detecting radiological changes in rheumatoid arthritis that are considered important by clinical experts: influence of reading with or without known sequence. J Rheumatol 2002;29(11):2306-2312.
78. Bruynesteyn K, van der Heijde D, Boers M et al. Determination of the minimal clinically important difference in rheumatoid arthritis joint damage of the Sharp/van der Heijde and Larsen/Scott scoring methods by clinical experts and comparison with the smallest detectable difference. Arthritis Rheum 2002;46(4):913-920.
79. van den Broek M, Dirven L, de Vries-Bouwstra JK et al. Rapid radiological progression in the first year of early rheumatoid arthritis is predictive of disability and joint damage progression during 8 years of follow-up. Ann Rheum Dis 2012 Sep;71(9):1530-3
80. Visser K, Goekoop-Ruiterman YP, de Vries-Bouwstra JK et al. A matrix risk model for the prediction of rapid radiographic progression in patients with rheumatoid arthritis receiving different dynamic treatment strategies: post hoc analyses from the BeSt study. Ann Rheum Dis 2010;69(7):1333-1337.
81. Emery P, Fleischmann R, van der Heijde D et al. The effects of golimumab on radiographic progression in rheumatoid arthritis: results of randomized controlled studies of golimumab before methotrexate therapy and golimumab after methotrexate therapy. Arthritis Rheum 2011;63(5):1200-1210.
82. Jensen T, Klarlund M, Hansen M et al. Bone loss in unclassified polyarthritis and early rheumatoid arthritis is better detected by digital x ray radiogrammetry than dual x ray absorptiometry: relationship with disease activity and radiographic outcome. Ann Rheum Dis 2004;63(1):15-22.
83. Brook A, Corbett M. Radiographic changes in early rheumatoid disease. Ann Rheum Dis 1977;36(1):71-73.
84. Haugeberg G, Green MJ, Quinn MA et al. Hand bone loss in early undifferentiated arthritis: evaluating bone mineral density loss before the development of rheumatoid arthritis. Ann Rheum Dis 2006;65(6):736-740.
85. Forslind K, Boonen A, Albertsson K, Hafstrom I, Svensson B. Hand bone loss measured by digital X-ray radiogrammetry is a predictor of joint damage in early rheumatoid arthritis. Scand J Rheumatol 2009;38(6):431-438.
86. Hoff M, Haugeberg G, Odegard S et al. Cortical hand bone loss after 1 year in early rheumatoid

arthritis predicts radiographic hand joint damage at 5-year and 10-year follow-up. Ann Rheum Dis 2009;68(3):324-329.

87. Guler-Yuksel M, Klarenbeek NB, Goekoop-Ruiterman YP et al. Accelerated hand bone mineral density loss is associated with progressive joint damage in hands and feet in recent-onset rheumatoid arthritis. Arthritis Res Ther 2010;12(3):R96.
88. Dirven L, Guler-Yuksel M, de Beus WM et al. Changes in hand bone mineral density and the association with the level of disease activity in patients with rheumatoid arthritis: bone mineral density measurements in a multicenter randomized clinical trial. Arthritis Care Res (Hoboken) 2011;63(12):1691-1699.
89. Keith MP, Edison JD, Gilliland WR. Progress toward personalized treatment of rheumatoid arthritis. Clin Pharmacol Ther 2012;92(4):440-442.
90. Allaart CF, Huizinga TW. Treatment strategies in recent onset rheumatoid arthritis. Curr Opin Rheumatol 2011;23(3):241-244.
91. van den Broek M, Visser K, Allaart CF, Huizinga TW. Personalized medicine: predicting responses to therapy in patients with RA. Curr Opin Pharmacol 2013;13(3):463-469.
92. Raychaudhuri SP, Nguyen CT, Raychaudhuri SK, Gershwin ME. Incidence and nature of infectious disease in patients treated with anti-TNF agents. Autoimmun Rev 2009;9(2):67-81.
93. Visser K, Verpoort KN, van Dongen H et al. Pretreatment serum levels of anti-cyclic citrullinated peptide antibodies are associated with the response to methotrexate in recent-onset arthritis. Ann Rheum Dis 2008;67(8):1194-1195.
94. Klaasen R, Wijbrandts CA, Gerlag DM, Tak PP. Body mass index and clinical response to infliximab in rheumatoid arthritis. Arthritis Rheum 2011;63(2):359-364.
95. Korpela M, Laasonen L, Hannonen P et al. Retardation of joint damage in patients with early rheumatoid arthritis by initial aggressive treatment with disease-modifying antirheumatic drugs: five-year experience from the FIN-RACo study. Arthritis Rheum 2004;50(7):2072-2081.
96. Klarenbeek NB, Guler-Yuksel M, van der Heijde DM et al. Clinical synovitis in a particular joint is associated with progression of erosions and joint space narrowing in that same joint, but not in patients initially treated with infliximab. Ann Rheum Dis 2010;69(12):2107-2113.

CHAPTER 2

FIVE YEAR OUTCOMES OF PROBABLE RHEUMATOID ARTHRITIS TREATED WITH METHOTREXATE OR PLACEBO DURING THE FIRST YEAR (THE PROMPT STUDY)

Ann Rheum Dis 2014 73(2):396-400

L. Heimans*, J. van Aken*, H. Gillet-van Dongen, K. Visser,
H.K. Ronday, I.Speyer, A.J. Peeters, T.W.J. Huizinga, C.F. Allaart

*Both authors contributed equally

ABSTRACT

Objective: To assess long-term disease outcome of undifferentiated arthritis (UA) after initial treatment with methotrexate (MTX) or placebo.

Methods: 110 patients with UA were randomised to receive MTX (n=55) or placebo (n=55) for 1 year. After 5 years the outcomes for diagnosis (rheumatoid arthritis, 1987 criteria (RA (1987)), UA or UA in remission) and radiographic progression were compared between treatment arms and anti-citrullinated protein antibody (ACPA)-positive and -negative patients. Outcomes were recalculated for patients who, with hindsight, might have been classified at baseline as having RA according to the 2010 criteria (RA (2010)).

Results: 25 patients in the MTX group and 29 in the placebo group progressed to RA (1987) (p=0.45). MTX delayed progression from UA to RA (1987) but only in ACPA-positive patients. Drug-free remission was achieved in 35 patients, 20 of whom were initially treated with MTX, and 32 were ACPA-negative. ACPA-positive patients had more radiographic progression, regardless of treatment. Forty-three patients (39%) could be reclassified as having had RA (2010) at baseline, 6/24 (25%) of whom achieved remission after placebo treatment.

Conclusions: After 5 years there is no lasting benefit of a 1 year initial course of MTX for patients with undifferentiated arthritis, compared with initial placebo. Progression to classifiable RA was not suppressed, drug-free remission not induced and the progression of radiological damage was similar in both groups. Reclassification at baseline with the 2010 criteria showed that 25% of patients with RA (2010) achieved spontaneous drug-free remission.

INTRODUCTION

Patients with inflammatory arthritis may present with undifferentiated arthritis (UA) not fulfilling any classification criteria.[1] Although UA may be a self-limiting disease, a considerable proportion of patients with UA has an early manifestation of rheumatoid arthritis (RA). For patients with recent-onset RA, a timely start of treatment with disease-modifying antirheumatic drugs (DMARDs) has proved to be crucial for achieving better clinical and radiographic outcomes. Therefore starting antirheumatic treatment already in UA might result in even more sustained benefits and potentially a chance for cure.[2, 3]

In the PROMPT study, we showed that treatment with methotrexate (MTX) compared with placebo for 1 year did not prevent, but (in anti-citrullinated protein antibody (ACPA)-positive patients at least) delayed, the development of UA into RA.[4] MTX reduced signs and symptoms at 12 months and radiographic progression at 18 months—again, particularly in ACPA-positive patients with UA. It remains to be determined whether this very early introduction of MTX has benefits in the long term.

In this study, the effect of early MTX treatment on clinical and radiological outcomes was assessed after 5 years. In addition, we identified predictors for disease progression to classifiable RA and for persistent remission in patients with UA. Finally, we re-evaluated current and previous study results using the 2010 classification criteria for RA to see whether MTX monotherapy in patients who fulfil the 2010 criteria and have relatively low disease activity is sufficient to achieve remission.[5]

PATIENTS AND METHODS

Study setting and design

The PROMPT study is a prospective double-blind, randomised, placebo-controlled multicentre trial evaluating the effect of 1 year MTX versus placebo treatment.[4] All 110 patients fulfilled the 1958 classification criteria for probable RA[6], were DMARD-naïve and had a symptom duration of <2 years.

Patients started treatment with MTX 15 mg/week (6 tablets of 2.5 mg) or the equivalent number of placebo tablets. No other DMARDs or steroids were allowed during the first year of treatment. Every 3 months, medication was increased by 5 mg MTX or two tablets placebo to a maximum of 30 mg or 12 tablets placebo a week as long as the Disease Activity Score (DAS) was >2.4. As soon as a patient fulfilled the 1987 ACR classification criteria for RA[7] (RA (1987)) during the first year, medication was switched to open-label MTX. After 12 months, the study drug was tapered and discontinued in the patients who had not developed RA (1987). IgM rheumatoid factor (RF) and ACPA were measured retrospectively in serum samples taken at baseline using commercial kits (Euro-Diagnostica, Arnhem, The Netherlands). ACPA levels >25 U/ml and RF levels >5 IU/ml were considered positive. Further details of the study and results of the primary outcomes have been published elsewhere.

To substantiate the PROMPT study results, the patients were reclassified at baseline according to the 2010 American College of Rheumatology/ European League Against Rheumatism (ACR)/EULAR criteria for RA.

Outcomes

At 3, 6, 9, 12, 30 and 60 months the diagnosis was recorded as classifiable RA (1987)[7] or UA (UA not fulfilling the 1987 ACR criteria), drug-free remission (DFR) without progression to RA (1987) or other (lost to follow-up or other diagnosis). Remission was defined as a DAS≤1.6[8] or the absence of synovitis or self-reported absence of symptoms without use of DMARDs. Radiographs of the hands and feet were obtained at inclusion and at 6, 12, 18, 30 and 60 months. Radiographic progression was scored by two independent readers using the Sharp–van der Heijde scoring (SHS) method[9] with radiographs blinded for patient identity, treatment group and time order.

Statistical analysis

Baseline and disease characteristics were compared between the two treatment arms, between ACPA-positive and ACPA-negative patients and between patients with RA (1987) and patients in DFR using the χ^2 test, Student's *t* test and the Mann–Whitney U test. To assess differences in time to reach one of the endpoints (RA (1987) or DFR), Kaplan–Meier curves with a log rank test were used.

In a large proportion of patients the readers independently scored no radiological damage progression (71% and 73%, respectively). Consequently, interobserver and intraobserver intraclass correlation coefficients were not suitable for measuring reliability.[10] In 71% of patients both readers scored the same progression. A consensus score was reached for the radiographs with inter-reader differences ≥1, based on a median (IQR) difference in progression score between readers of 0 (0–2). The mean score of the readers was used for the analyses. We performed a completers' analysis, then repeated the analyses with imputed values according to last observation carried forward, for incomplete series.

Univariate logistic regression analysis was used to identify potential predictors for fulfilling the criteria of RA (1987) after 60 months and for DFR, including age, sex, symptom duration, baseline SHS, baseline erosion score, baseline DAS, baseline Health Assessment Questionnaire, ACPA status and RF status. The univariate predictors that reached statistical significance ($p \leq 0.1$) were entered stepwise in a multivariate model. Age and gender, as known predictors, were forced into the model. To avoid problems of colinearity, separate analyses were done with either ACPA or RF.

RESULTS

After 5 years, seven patients were lost to follow-up because they had either moved away or had died. Radiographs after 5 years were obtained for 67 patients.

Baseline and disease characteristics of the 110 patients with UA (55 receiving MTX, 55 placebo) are shown in table 1.

Diagnosis at 60 months

1987 RA criteria

After 60 months 54/110 patients (49%) had disease progression and fulfilled the 1987 RA classification criteria. In the MTX group 25/55 patients (45%) progressed to RA (1987), in the placebo group 29/55 (53%) patients (p=0.45) (table 2). All the 29 patients in the placebo group who progressed to RA (1987) did so within 1 year, compared with 11/25 in the MTX group. Yet, possibly owing to small numbers, Kaplan–Meier analyses showed no significant difference in time to progression to RA between the treatment groups (p=0.11) (figure 1A). Of the patients who progressed to RA (1987), the 25 patients in the MTX group used a median of 1 (1–2) DMARDs in 5 years, compared with a median of 2 (1–3) DMARDs in the 29 patients of the placebo group. ACPA-positive patients progressed significantly faster to RA (1987) than ACPA-negative patients (p<0.001). Initial MTX treatment delayed progression to RA (1987) in the ACPA-positive group but not in the ACPA-negative group (p<0.001) (figure 1B,C).

Drug-free remission and persistent UA

In the MTX group 25/55 patients (45%) did not progress to RA (1987). At 5 years, of those 25 patients, 19 were in persistent DFR since 1 year, and one was in DFR after using hydroxychloroquine for 35 months. Five were still diagnosed as having active UA (table 2). In the placebo group 17/55 (31%) patients did not progress to RA (1987) and 15 were in DFR after 60 months, two still had arthritis (table 2). None of these 15 patients had used DMARDs since 1 year. Of the total group, 35/110 patients (32%) were

Table 1. Baseline and disease characteristics for both randomization groups.

	MTX (n=55)	Placebo (n=55)	p
Age in years	51 (42-60)	51.3 (42-56)	0.39
Female	35 (64)	38 (69)	0.55
Symptom duration in days	312 (195-507)	263 (169-432)	0.29
Morning stiffness in minutes	30 (10-60)	30 (10-60)	0.95
RF positive	20 (36)	19 (35)	0.96
ACPA positive	12 (22)	15 (27)	0.51
DAS	2.72 (0.78)	2.52 (0.76)	0.19
HAQ	0.79 (0.51)	0.78 (0.58)	0.90
Sharp-van der Heijde score	0 (0-2)	0 (0-2)	0.93
Fulfilled ACR-EULAR 2010 RA criteria	19 (35)	24 (44)	0.33

Data are presented as means ± standard deviations (SD), medians and interquartile ranges (IQR), or numbers and percentages (%) when appropriate. RF: rheumatoid factor, ACPA: anti-citrullinated protein antibody, HAQ: Health Assessment Questionnaire, DAS: disease activity score, SHS: Sharp-van der Heijde score, RA: Rheumatoid Arthritis.

in DFR at 60 months. The survival analysis did not show a difference in time to achieve DFR between the MTX and the placebo group (p=0.34) (figure 1D). Most patients who achieved DFR were ACPA negative (32/35), and achieved DFR significantly earlier than the three ACPA-positive patients (p=0.008).

2010 RA criteria

Based on signs and symptoms, 43/110 patients with UA (39%) fulfilled the 2010 ACR/EULAR classification criteria for RA (RA (2010)) at baseline (table 1). Nineteen of these patients were randomised to the MTX group. Of these patients, 12/19 (63%) had disease progression to fulfilling the 1987 classification criteria, 5/19 (26%) achieved DFR. Of the 24 RA (2010) patients randomised to the placebo group, 17/24 (71%) progressed to RA (1987) and 6/24 (25%) achieved DFR.

Predictors of drug-free remission and fulfilling the criteria for RA

The univariate predictors for fulfilling the 1987 classification for RA after 60 months were, separately tested, ACPA positivity (OR=9.7, 95% CI 3.1 to 30.5) and RF positivity (OR=3.0, 95% CI 1.3 to 6.8). Multivariate analyses including ACPA or RF, age, gender, SHS and DAS at baseline, showed ACPA (OR=8.9 95% CI 2.7 to 29.1), SHS at baseline (OR=1.3,

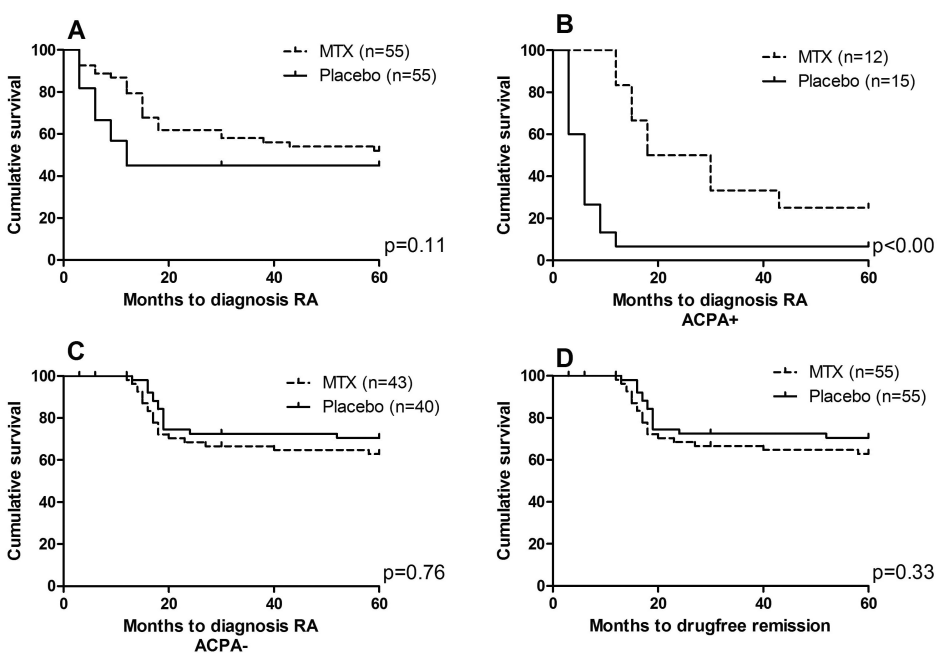

Figure 1. Kaplan-Meier survival analysis for (A) the time to diagnosis of rheumatoid arthritis in the total group, (B) in ACPA (anti-citrullinated protein antibody)-positive patients, (C) in ACPA-negative patients, (D) the time to drug free remission in the total group. MTX: methotrexate, ACPA: anti-citrullinated protein antibody.

Table 2. Diagnosis after 30 and 60 months follow up in patients initially treated with 1 year MTX or 1 year placebo.

	30 months		60 months	
Diagnosis	**MTX**	**Placebo**	**MTX**	**Placebo**
RA (1987 criteria)	22	29	25	29
UA (active arthritis)	10	4	5	2
Drug free remission	15	13	20	15
Other diagnosis	3*	4**	3*	4**
Lost to follow up	5	5	2	5
Total	55	55	55	55

Values indicate the number of patients.
* 2 osteoarthritis, 1 autoimmune hepatitis. ** 3 osteoarthritis and 1 diabetic arthropathy. RA: rheumatoid arthritis, UA: undifferentiated arthritis, DFR: patients in drug free remission without progression to RA.

95% CI 1.01 to 1.6) and RF (OR=2.9, 95% CI 1.2 to 7.1) as independent predictors for progression to RA (1987).

Absence of ACPA (OR=5.0, 95% CI 1.4 to 18.0) was identified as the only independent predictor for DFR (OR=5.1, 95% CI 1.4 to 18.5, in the multivariate analysis including ACPA, age and gender).

Radiographic damage

Completers

After 60 months, 67 patients had completed the radiographic follow-up. Patients who completed follow-up were more often ACPA positive (36% versus 7% in non-completers) and more had progressed to RA (1987) (66% versus 23% in non-completers). In 39/67 patients (58%) there was no radiological progression at all. Radiological damage progression was comparable in patients who had progressed to RA (1987) and those who were in DFR after 5 years (p=0.08). There was significantly more damage progression in the ACPA-positive than in the ACPA-negative patients (median (IQR) 1.8 (0–6) versus 0 (0–0.5); p=0.001).

Total group

Imputation of missing values by last observation carried forward was done in 107 patients (no imputation in three patients with only baseline scores). In 73/110 (66%) patients were estimated to have no progression. In the 34 patients who showed progression, median progression was 2 (1–7). The median (IQR) progression of patients initially treated with MTX was 0 (0–1) and in the placebo group 0 (0–1) (p=0.78). After 5 years, patients who progressed to RA (1987) had more progression than patients in DFR (respectively 0 (0–2) versus 0 (0–0); p=0.02). Again, ACPA-positive patients showed more radiological progression than ACPA-negative patients (1.5 (0–3) points progression in SHS versus 0 (0–0), p<0.001), regardless of initial treatment (figure 2). Two ACPA-positive patients who initially received placebo showed rapid radiological progression, defined

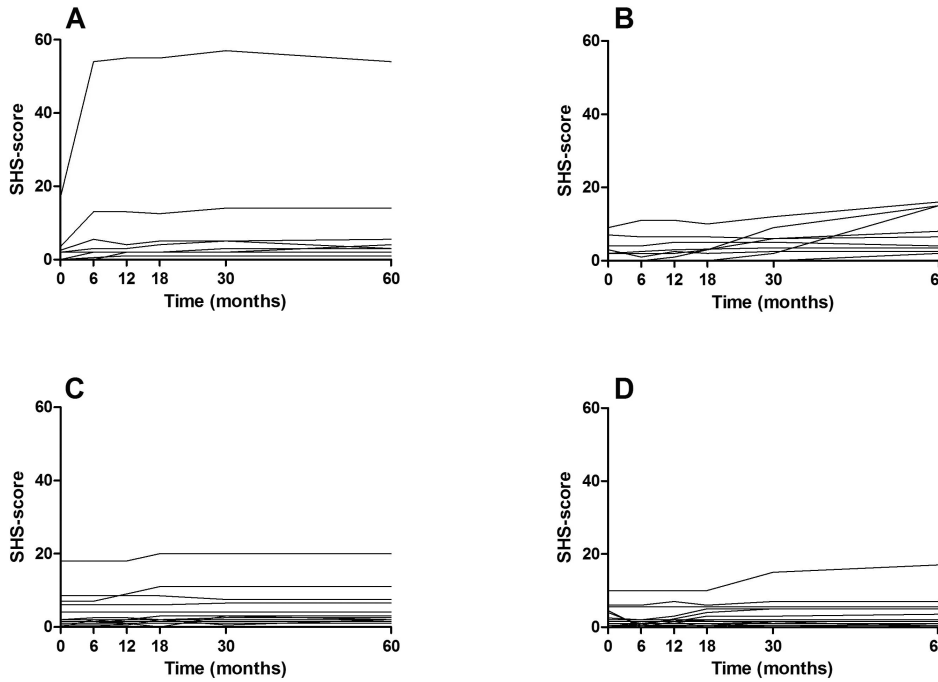

Figure 2. Sharp- van der Heijde Score at every time point for individual patients who were either A) anti-citrullinated protein antibody (ACPA) positive and treated with placebo (n=15), B) ACPA positive and treated with MTX (n=12), C) ACPA negative and treated with placebo (n=40), or D) ACPA negative and treated with MTX (n=43). SHS: Sharp-van der Heijde Score, MTX: methotrexate, ACPA: anti-citrullinated protein antibody.

as an increase in SHS of ≥5 points in year 1 (figure 2A).[77, 78] None of the other patients showed rapid radiological progression.

DISCUSSION

The PROMPT study, a randomised clinical trial in patients with UA, was set up to establish whether very early treatment with MTX could induce drug-free remission or prevent progression to RA (1987). Early study results showed that MTX can postpone progression from UA to RA and suppresses radiological damage progression, in particular in ACPA-positive patients.[4] In this study we have found that after 5 years there is little lasting benefit of early MTX treatment. Overall, patients with UA treated with MTX did not achieve more DFR, did not progress less often to RA (1987) and had comparable damage progression compared with patients with UA who initially were treated with placebo. Only in ACPA-positive patients did initial MTX postpone progression to RA (1987). These results indicate that early treatment with MTX is ineffective in altering the disease course of UA. This may be owing to inefficacy of the drug, duration of treatment, characteristics of the targeted illness, inadequate timing of treatment, or all of the above.

MTX may be seen as the cornerstone of antirheumatic treatment,[13, 14] yet MTX monotherapy as initial treatment in patients with RA is often inferior to initial combination treatment with corticosteroids or biological DMARDs.[15-18] It may be that such initial combination treatment in our population would have been more successful in altering the disease course than MTX monotherapy. It is also possible that discontinuation of MTX after 1 year was too soon, but longer treatment cannot be seen as induction therapy, which was the target of the PROMPT study.

The finding that initial treatment with MTX delayed progression to 1987 classifiable RA only in ACPA-positive patients suggests that the effect of treatment may depend on the type of illness presenting as UA. We found that ACPA and RF are independent predictors for disease progression to RA (1987) after 60 months. Time to progress to RA (1987) was significantly shorter in ACPA-positive patients than in the ACPA-negative patients. Absence of ACPA was the only independent predictor of drug-free remission after 5 years. ACPA-positive patients showed more radiographic progression, despite the fact that having progressed to classifiable RA many started treatment with open-label MTX, after which damage progression was suppressed. Overall, we found no difference in radiographic progression between the MTX- or placebo-treated groups. These results suggest that ACPA-positive and ACPA-negative early arthritis are different disease entities, which may require different treatments. In addition, the persistence of remission in the majority of ACPA-negative patients (also those treated with placebo) suggests that these had a temporary disease, which could not be identified at presentation, by symptom duration or characteristics other than ACPA status.

It might be that we started initial treatment with MTX too late. We included and treated patients who were at the time considered to have UA, but who now would be classified as RA, based on the 2010 classification criteria for RA.[5] In retrospect, 43 patients (39%) of the patients included as UA fulfilled the 2010 ACR/EULAR criteria at baseline, 23 of whom were ACPA positive. It is possible that for these patients the opportunity to achieve a change in the disease course by whatever treatment, might already have been lost. On the other hand, the new criteria may also misclassify some patients as having RA, and lead to overtreatment. Twenty-four of the 43 patients fulfilling the 2010 criteria were randomised to initial placebo treatment, and six of those 24 achieved clinical remission. This means that, had we started MTX in all patients who fulfilled the 2010 criteria, we would have overtreated these six patients (25%). We also started MTX treatment in 36 patients who in retrospect did not fulfil the 2010 classification criteria, which may also qualify as overtreatment. Of these patients, 13 did progress to RA (1987), which more effective treatment might have prevented.

In summary, in this randomised clinical trial comparing the outcomes after 5 years of initial MTX treatment and placebo in patients with UA, there is no lasting effect of MTX treatment given in the first year. A positive ACPA status and radiological damage at baseline are independent predictors for progression to RA and a negative ACPA status is a predictor for DFR. The observed rate of spontaneous remission, particularly in the ACPA-negative

patients, demonstrates that initiation of MTX treatment in all patients who fulfil the 2010 ACR/EULAR criteria would constitute overtreatment in 25% of patients. On the other hand, mostly in ACPA-positive patients, initial MTX monotherapy is insufficient to prevent disease progression. Further research should focus on early and correct recognition of RA, as well as identifying a treatment that might truly alter the disease process.

REFERENCE LIST

1. Schumacher HR. Early arthritis clinics. Much early arthritis is unclassified. J Rheumatol 2002;29(11):2258-2260.
2. Finckh A, Liang MH, van Herckenrode CM et al. Long-term impact of early treatment on radiographic progression in rheumatoid arthritis: A meta-analysis. Arthritis Rheum 2006;55(6):864-872.
3. van der Linden MP, le Cessie S, Raza K et al. Long-term impact of delay in assessment of patients with early arthritis. Arthritis Rheum 2010;62(12):3537-3546.
4. van Dongen H, van Aken J, Lard LR et al. Efficacy of methotrexate treatment in patients with probable rheumatoid arthritis: a double-blind, randomized, placebo-controlled trial. Arthritis Rheum 2007;56(5):1424-1432.
5. Aletaha D, Neogi T, Silman AJ et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/ European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010;69(9):1580-1588.
6. Ropes MW, Bennett GA, Cobb S et al. 1958 Revision of diagnostic criteria for rheumatoid arthritis. Bull Rheum Dis 1958;9(4):175-176.
7. Arnett FC, Edworthy SM, Bloch DA et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31(3):315-324.
8. Prevoo ML, van Gestel AM, van 't Hof M et al. Remission in a prospective study of patients with rheumatoid arthritis. American Rheumatism Association preliminary remission criteria in relation to the disease activity score. Br J Rheumatol 1996;35(11):1101-1105.
9. van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. J Rheumatol 2000;27(1):261-263.
10. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. Psychol Bull 1979;86(2):420-428.
11. Bruynesteyn K, van der Heijde D, Boers M et al. Determination of the minimal clinically important difference in rheumatoid arthritis joint damage of the Sharp/van der Heijde and Larsen/Scott scoring methods by clinical experts and comparison with the smallest detectable difference. Arthritis Rheum 2002;46(4):913-920.
12. Bruynesteyn K, van der Heijde D, Boers M et al. Detecting radiological changes in rheumatoid arthritis that are considered important by clinical experts: influence of reading with or without known sequence. J Rheumatol 2002;29(11):2306-2312.
13. Pincus T, Yazici Y, Sokka T et al. Methotrexate as the "anchor drug" for the treatment of early rheumatoid arthritis. Clin Exp Rheumatol 2003;21(5 Suppl 31):S179-S185.
14. Smolen JS, Landewe R, Breedveld FC et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis 2010;69(6):964-975.
15. de Jong PH, Hazes JM, Barendregt PJ et al. Induction therapy with a combination of DMARDs is better than methotrexate monotherapy: first results of the tREACH trial. Ann Rheum Dis. 2013;72(1):72-8.
16. Landewe RB, Boers M, Verhoeven AC et al. COBRA combination therapy in patients with early rheumatoid arthritis: long-term structural benefits of a brief intervention. Arthritis Rheum 2002;46(2):347-356.
17. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): A randomized, controlled trial. Arthritis Rheum 2008;58(2 Suppl):S126-S135.
18. Mottonen T, Hannonen P, Leirisalo-Repo M et al. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. Lancet 1999;353(9164):1568-1573.

CHAPTER 3

REMISSION INDUCTION THERAPY WITH METHOTREXATE AND PREDNISONE IN PATIENTS WITH EARLY RHEUMATOID AND UNDIFFERENTIATED ARTHRITIS

Ann Rheum Dis 2012 71(9):1472-7

K.V.C. Wevers-de Boer, K. Visser, L. Heimans, H.K. Ronday,
T.H.E. Molenaar, J.H.L.M. van Groenendael, A.J. Peeters, M.L. Westedt,
G. Colleé, P.B.J. de Sonnaville, B.A.M Grillet, T.W.J. Huizinga, C.F. Allaart

ABSTRACT

Aim: Classifying more patients as rheumatoid arthritis (RA) (2010 American College of Rheumatology/European League Against Rheumatism criteria for RA) may improve treatment outcomes but may cause overtreatment in daily practice. The authors determined the efficacy of initial methotrexate (MTX) plus prednisone treatment in patients with 1987 or 2010 classified RA and undifferentiated arthritis (UA).

Methods: 610 recent onset RA or UA patients started with MTX 25 mg/week and prednisone 60 mg/day tapered to 7.5 mg/day in 7 weeks. Percentage remissions 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 211/264 (58%) 1987 classified RA patients ($p=0.52$), and 79/122 (65%) UA patients ($p=0.46$). Anti-citrullinated protein antibody (ACPA) positive RA patients achieved more remission (66%) than ACPA negative RA patients (51%, $p=0.001$), but also had a lower mean baseline Disease Activity Score (DAS) (3.2 versus 3.6, $p<0.001$). Independent predictors for remission were male sex, low joint counts, DAS and Health Assessment Questionnaire, low body mass index and ACPA positivity.

Conclusions: Initial treatment with MTX and a tapered high dose of prednisone results in similarly high remission percentages after 4 months (about 60%) in RA patients, regardless of fulfilling the 1987 or 2010 criteria, and in 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 with 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 hypothesised 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 and placebo groups.[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 antirheumatic drug 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.

PATIENTS AND METHODS

Study design

The IMPROVED study is a multicentre, clinical trial in recent onset RA and UA patients. 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 in 7 weeks to 7.5 mg/day, and continued in this dose up to 4 months. Later, this introduction phase will be followed by a single blind randomised 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 and the other with a combination of MTX with adalimumab.

Rheumatologists participating in the Foundation for Applied Rheumatology Research 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/subjects

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 disease modifying antirheumatic drugs or corticosteroids, pregnancy or pregnancy wish during the study, malignancy within the last 5 years, bone marrow hypoplasia, elevated liver enzyme levels (aspartate transaminase (AST) and/or alanine transaminase (ALT)>3 times the normal value), serum creatinine level >150 umol/l or estimated creatinine clearance of <75%, uncontrolled diabetes mellitus, uncontrolled hypertension, heart failure (New York Heart Association 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 antituberculous 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 4 months were percentage clinical remission, defined as a DAS<1.6, 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.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 interobserver and intraobserver intraclass correlation coefficients 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).

Percentage remissions according to ACR/European League Against Rheumatism (EULAR) preliminary definition[20]were compared with percentage remissions 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 the χ^2 test. Categorical variables were compared between groups using the χ^2 test, normally distributed outcome measures with the independent samples t-test and skewed outcome measures using the 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: two patients because of a revised diagnosis (one osteoarthritis, one lupus), two because of comorbidity, six withdrew consent and two died (figure 1).

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

Inclusion *1987 criteria,* n (%)	RA (1987): 364 (60%)	UA: 246 (40%)
Reclassification *2010 criteria,* n (%)*	RA (2010): 479 (79%)	UA (2010):122 (20%)
	RA(2010)	UA(2010)
RA (1987), n (%)	324/364 (89%)	34/364 (9%)
UA n (%)	155/246 (63%)	88/246 (36%)

RA(1987): RA according to the 1987 classification criteria for RA.[8] UA: at least one swollen and one painful joint, at risk of 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.[9] UA(2010): included in trial as RA(1987) or UA, not fulfilling the 2010 classification criteria for RA
*9 patients could not be classified because of insufficient data.

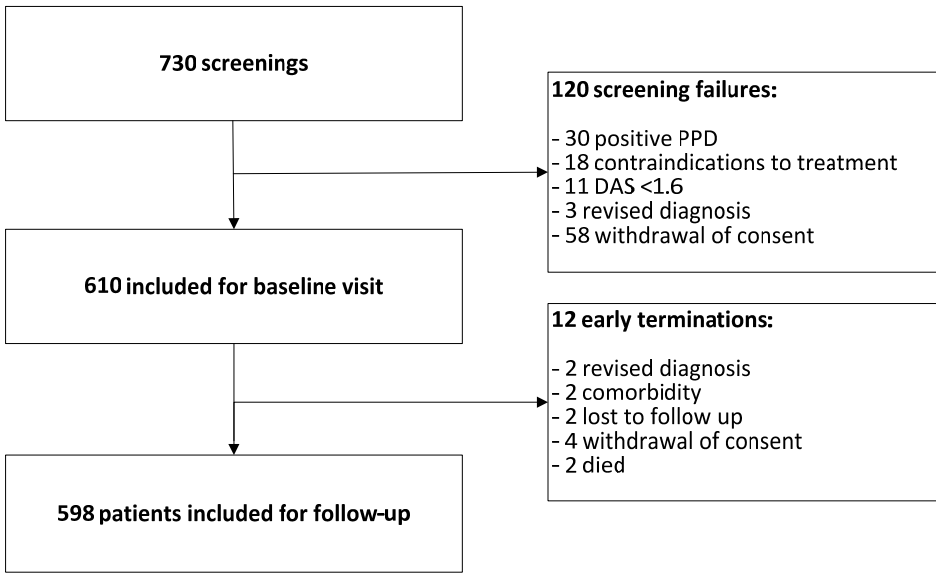

Figure 1. Flow chart of screenings failure and early terminations. PPD: purified protein derivative, DAS: Disease Activity Score.

Baseline characteristics

RA (1987) patients had a higher mean DAS based on more affected joints, higher erythrocyte sedimentation rate and higher serum C-reactive protein than RA (2010) patients. UA patients included fewer female subjects, were less often rheumatoid factor and anti-citrullinated protein antibody (ACPA) positive, and 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 4 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 with RA 2010).

DAS improved more in the RA (2010) group than in the UA group and was 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-month radiographs of hands and feet were available for 546 patients. After 4 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) point.

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

Table 2. Baseline characteristics and clinical outcomes after 4 months of RA patients classified either by 1987 or 2010 criteria and of UA patients.

Baseline	RA1987 n=364	RA2010 n=479	UA p-value*	UA n=122	UA p-value**
Age, years mean ± SD	53.5 (14)	52 (13)	0.08	52 (16)	0.90
Female, n (%)	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, n (%)	254 (67)	330 (69)	0.59	5 (4)	<0.001
ACPA positive, n (%)	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 (6-36)	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, n (%)	49 (13)	60 (13)	0.62	12 (9)	0.46
Follow up (4 months)					
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, n (%)	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), n (%)	211 (58)	291 (61)	0.52	79 (65)	0.46

SD: standard deviation, IQR: interquartile ranges, n: number, RF: rheumatoid factor, ACPA: anti-citrullinated protein antibody, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, DAS: disease activity score, HAQ: Health Assessment Questionnaire, BMI: body mass index, SHS: Sharp- van de Heijde Score, SHS progression: increase in SHS ≥0.5 points, remission: DAS<1.6.[16] Erosive denotes the presence of at least 1 erosion on radiographs of hands and feet. * p-value based on difference between RA1987 and RA2010. ** p-value based on difference between RA2010 and UA.

who did achieve remission (table 3). Of the ACPA positive RA patients, 66% achieved remission compared with 51% of the ACPA negative RA patients (p=0.001). ACPA positive RA patients had 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 with 94% of the UA patients

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

Baseline	Remission n=375	No remission n=221	p-value
DAS, mean ± SD	2.99 (0.85)	3.57 (0.92)	<0.001
Swollen joint count, median (IQR)	5 (2-9)	7 (3-12)	0.001
Tender joint count, median (IQR)	5 (3-8)	8 (6-14)	<0.001
VAS general health in 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, n (%)	231 (62)	172 (78)	<0.001
RF positive, n (%)	219 (58)	111 (50)	0.09
ACPA positive, n (%)	220 (59)	106 (48)	0.007
Diagnosis RA(2010), n (%)	291 (78)	177 (80)	0.46
BMI, mean ± SD	25.4 (3.9)	26.6 (5.1)	0.001
Follow up (4 months)			
DAS, mean ± SD	0.94 (0.36)	2.45 (0.65)	<0.001
Swollen joint count, median (IQR)	0 (0-0)	1 (0-4)	<0.001
Tender joint count, median (IQR)	0 (0-1)	4 (3-8)	<0.001
VAS general health in 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

Remission: DAS<1.6.[16] SD: standard deviation, IQR: interquartile ranges, n: number, DAS: disease activity score, VAS: visual analogue scale, ESR: erythrocyte sedimentation rate, HAQ: Health Assessment Questionnaire, RF: rheumatoid factor, ACPA: anti-citrullinated protein antibody, RA(2010): rheumatoid arthritis according to the 2010 classification criteria, BMI: body mass index.
*number of swollen and/or tender small joints (metacarpophalangeal joints, proximal interphalangeal joints, thumb interphalangeal joinst, wrists, second through fifth metacarpophalangeal joints)
** number of swollen and/or tender large joints (schoulders, elbows, hips, knees, ankles)

(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 remission less often 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 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 for 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,[57] 157/610 (26%) of the patients achieved remission after 4 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 4 months of patients in ACR/EULAR remission is 0.82 (0.41).

Table 4. Univariate and multivariate logistic regression analyses with remission as dependent variable

Univariate regression	**Odds ratio**	**95% CI**
Classified RA	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 (wks)	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

	Analysis with DAS		**Analysis with small and large joints**	
Multivariate regression	**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 (wks)	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

Classified RA: rheumatoid arthritis according to the 2010 classification criteria for RA, DAS: disease activity score, HAQ: Health Assessment Questionnaire, ACPA: anti-citrullinated protein antibody, BMI: body mass index.
*number of swollen and/or tender small joints (metacarpophalangeal joints, proximal interphalangeal joints, thumb interphalangeal joinst, wrists, second through fifth metacarpophalangeal joints)
** number of swollen and/or tender large joints (schoulders, elbows, hips, knees, ankles)

In all, 206/610 (34%) patients did achieve DAS remission but were not in ACR/EULAR remission. They had a median (IQR) tender joint count of 0 (0–1), a median (IQR) swollen joint count of 0 (0–0), a median (IQR) C-reactive protein of 5 (3–9) and a mean (SD) Visual Analogue Scale general health of 21 (14).

A total of 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 are 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 subject 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 subject 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 (three patients), viral pneumonitis, urothelial cell carcinoma, surgery for carcinoma of the caecum, 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 4 months. The majority (90%) of the patients showed no radiological progression after 4 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 COBRA (Combinatietherapie Bij Reumatoide Artritis) and BeSt (Behandel Strategieën), 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 overclassified patients who possibly had self-limiting disease.[8] Other possible

Table 5. numbers of adverse events reported during the first four 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

explanations are the initial dose of MTX (25 mg/week compared with 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 hypothesised that UA patients, as presumably very early RA, would benefit more from early combination therapy, and despite the fact that UA patients had a lower mean baseline disease activity and were predominantly male subjects. 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 with 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 PROMPT (Probable rheumatoid arthritis: Methotrexate versus Placebo Treatment) study ACPA negative UA patients did not benefit from treatment with MTX 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 BMI was found to be an independent predictor of remission, which may be related to relative underdosing of patients with a high BMI.

The early and intensive treatment with a high dose of MTX 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 older patients died, one from pneumonia that may have been treatment related and on the patient's request remained untreated, and 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 underdosed.

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 4 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.

REFERENCE LIST

1. Egsmose C, Lund B, Borg G et al. Patients with rheumatoid arthritis benefit from early 2nd line therapy: 5 year followup of a prospective double blind placebo controlled study. J Rheumatol 1995;22(12):2208-2213.
2. Finckh A, Liang MH, van Herckenrode CM, de Pablo P. Long-term impact of early treatment on radiographic progression in rheumatoid arthritis: A meta-analysis. Arthritis Rheum 2006;55(6):864-872.
3. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. Arthritis Rheum 2005;52(11):3381-3390.
4. Klarenbeek NB, Guler-Yuksel M, van der Kooij SM et al. The impact of four dynamic, goal-steered treatment strategies on the 5-year outcomes of rheumatoid arthritis patients in the BeSt study. Ann Rheum Dis 2011;70(6):1039-1046.
5. Lard LR, Visser H, Speyer I et al. Early versus delayed treatment in patients with recent-onset rheumatoid arthritis: comparison of two cohorts who received different treatment strategies. Am J Med 2001;111(6):446-451.
6. van der Heide A, Jacobs JW, Bijlsma JW et al. The effectiveness of early treatment with "second-line" antirheumatic drugs. A randomized, controlled trial. Ann Intern Med 1996;124(8):699-707.
7. Aletaha D, Neogi T, Silman AJ et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/ European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010;69(9):1580-1588.
8. Cader MZ, Filer A, Hazlehurst J, de Pablo P, Buckley CD, Raza K. Performance of the 2010 ACR/EULAR criteria for rheumatoid arthritis: comparison with 1987 ACR criteria in a very early synovitis cohort. Ann Rheum Dis 2011;70(6):949-955.
9. Ma MH, Scott IC, Kingsley GH, Scott DL. Remission in early rheumatoid arthritis. J Rheumatol. 2010 Jul;37(7):1444-53.
10. van Dongen H, van Aken J, Lard LR et al. Efficacy of methotrexate treatment in patients with probable rheumatoid arthritis: a double-blind, randomized, placebo-controlled trial. Arthritis Rheum 2007;56(5):1424-1432.
11. Boers M, Verhoeven AC, Markusse HM et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet 1997;350(9074):309-318.
12. Kirwan JR, Bijlsma JW, Boers M, Shea BJ. Effects of glucocorticoids on radiological progression in rheumatoid arthritis. Cochrane Database Syst Rev 2007;(1):CD006356.
13. Mottonen T, Hannonen P, Leirisalo-Repo M et al. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. Lancet 1999;353(9164):1568-1573.
14. Landewe RB, Boers M, Verhoeven AC et al. COBRA combination therapy in patients with early rheumatoid arthritis: long-term structural benefits of a brief intervention. Arthritis Rheum 2002;46(2):347-356.
15. Arnett FC, Edworthy SM, Bloch DA et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31(3):315-324.
16. Prevoo ML, van Gestel AM, van 't Hof MA, van Rijswijk MH, van de Putte LB, van Riel PL. Remission in a prospective study of patients with rheumatoid arthritis. American Rheumatism Association preliminary remission criteria in relation to the disease activity score. Br J Rheumatol 1996;35(11):1101-1105.
17. Siegert CE, Vleming LJ, Vandenbroucke JP, Cats A. Measurement of disability in Dutch rheumatoid arthritis patients. Clin Rheumatol 1984;3(3):305-309.
18. van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. J Rheumatol 2000;27(1):261-263.
19. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. Psychol Bull 1979;86(2):420-428.
20. Felson DT, Smolen JS, Wells G et al. American College of Rheumatology/European League against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Ann Rheum Dis 2011;70(3):404-413.
21. van der Linden MP, le Cessie S, Raza K et al. Long-term impact of delay in assessment of patients with early arthritis. Arthritis Rheum 2010;62(12):3537-3546.

22. Daha NA, Toes RE. Rheumatoid arthritis: Are ACPA-positive and ACPA-negative RA the same disease? Nat Rev Rheumatol. 2011 Apr;7(4):202-3

23. Katchamart W, Johnson S, Lin HJ, Phumethum V, Salliot C, Bombardier C. Predictors for remission in rheumatoid arthritis patients: A systematic review. Arthritis Care Res (Hoboken) 2010 Aug;62(8):1128-43

CHAPTER 4

A TWO-STEP TREATMENT STRATEGY TRIAL IN PATIENTS WITH EARLY ARTHRITIS AIMED AT ACHIEVING REMISSION: THE IMPROVED-STUDY

Accepted for publication in Annals of the Rheumatic Diseases

L. Heimans*, K.V.C. Wevers-de Boer*, K. Visser, R.J. Goekoop, M. van Oosterhout, J.B. Harbers, C. Bijkerk, I. Speyer, P.D.M. de Buck, P.B.J. de Sonnaville, B.A.M. Grillet, T.W.J. Huizinga, C.F. Allaart

*Both authors contributed equally

ABSTRACT

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

Methods: 610 patients with early rheumatoid arthritis (RA 2010 criteria) or undifferentiated arthritis (UA) started treatment with methotrexate (MTX) and a tapered high dose of prednisone. Patients in early remission (Disease Activity Score <1.6 after 4 months) tapered prednisone to zero and those with persistent remission after 8 months, tapered and stopped MTX. Patients not in early remission were randomised to receive either MTX plus hydroxychloroquine plus sulfasalazine plus low-dose prednisone (arm 1) or to MTX plus adalimumab (ADA) (arm 2). If remission was present after 8 months both arms tapered to MTX monotherapy; if not, arm 1 changed to MTX plus ADA and arm 2 increased the dose of ADA. Remission rates and functional and radiological outcomes were compared between arms and between patients with RA and those with UA.

Results: 375/610 (61%) patients achieved early remission. After 1 year 68% of those were in remission and 32% in drug-free remission. Of the randomised patients, 25% in arm 1 and 41% in arm 2 achieved remission at year 1 ($p<0.01$). Outcomes were comparable between patients with RA and those with UA.

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

INTRODUCTION

The way in which patients with rheumatoid arthritis (RA) are treated has changed dramatically over recent decades. Early and tightly controlled treatment with disease-modifying antirheumatic drugs (DMARDs), targeted at low disease activity, suppresses inflammation better than previously, resulting in improved functional ability and minimised radiological joint damage.[1-6] Even remission can be achieved. Early combination therapy with synthetic DMARD treatment plus prednisone or a tumour necrosis factor (TNF) alpha inhibitor is 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 from becoming chronic and damaging to bone and joint tissues. To enable earlier diagnosis and treatment initiation, classification criteria for rheumatoid arthritis (RA) were revised in 2010.[10] Starting antirheumatic treatment at the stage of undifferentiated arthritis (UA), when RA is still unclassifiable, might be useful.[7]

Treatment of patients with UA with methotrexate (MTX) was successful in postponing, but not preventing, progression to RA.[11] It is possible that, as in patients with RA, initial combination therapy with MTX and prednisone might be more effective.[8] If patients do not achieve remission with initial combination therapy, the best follow-up strategy needs to be determined: either expansion of DMARDs or switching to MTX with a TNF-alpha inhibitor; both proved effective in established RA.[6, 9]

We designed a two-step treatment strategy study (remission induction therapy followed by randomisation 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 MTX and Prednisone in Rheumatoid Or Very Early arthritic Disease, ISRCTN Register number 11916566 and EudraCT number 2006-006186-16) is a multicentre, randomised, single-blinded clinical trial designed by Dutch rheumatologists participating in the Foundation for Applied Rheumatology Research. Patients were recruited between March 2007 and September 2010 in 12 hospitals in the western area 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 inclusion and exclusion criteria have been previously published.[8] Recent-onset RA was defined according to the ACR/EULAR 2010 classification criteria,[10] with symptom duration ≤2 years. Patients with UA had at least one joint clinically assessed as 'arthritis' and at least one other tender joint, which the rheumatologist suspected to be early RA, but not fulfilling the 2010 ACR/EULAR criteria.

Intervention

The treatment target was clinical remission, defined as a Disease Activity Score (DAS)<1.6.[12] Four-monthly assessments of DAS were performed by trained nurses who were blinded to the allocated treatment. Patients and doctors were not blinded for practical reasons. All patients started with 4 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. If DAS was ≥1.6 after stopping prednisone, it was restarted at 7.5 mg/day (figure 1).

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

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

Variable block randomisation stratified for each centre and diagnosis ensured the same number in the two randomisation arms. Randomisation sequence was obtained

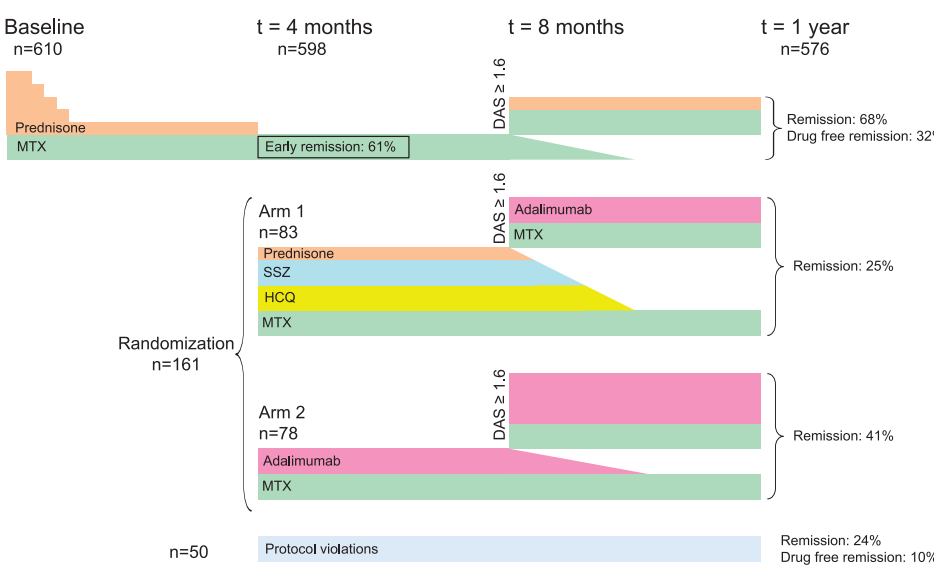

Figure 1. Study flow chart with percentages DAS-remission after the first study year. MTX: methotrexate, DAS: disease activity score, SSZ: sulfasalazine, HCQ: hydroxychloroquine, Remission: DAS≤1.6.

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 remission and DFR based on a DAS<1.6. A provisional Boolean-based remission definition, published by ACR/EULAR,[13] 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),[14] radiological damage progression measured with Sharp–van der Heijde score (SHS, ranging from 0 to 448, progression was defined as an increase in SHS≥0.5 point)[15] 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 two trained, independent readers (KW and LH). Since 88% of patients showed no progression, intraclass correlation coefficients were not suitable for measuring reliability.[16] 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 for which both readers scored different progression) a consensus score was reached.

Outcomes were reported separately for patients who achieved early DAS remission and those randomised, and were compared between randomisation arms. Additional comparisons were made between patients with RA and those with UA. Patients who were not in early DAS remission and who were not randomised according to the protocol were analysed in the outside of protocol (OP) group. Reasons for protocol deviation were not inventoried.

Statistical analysis

With a power calculation we assessed the number of patients needed in each randomisation 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,[6, 9, 17] we estimated that 30% of the patients would achieve early remission. We needed 535 patients to randomise at least 100 patients in each 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 a Student's *t* test, Mann–Whitney U tests and χ^2 tests. DAS and HAQ were compared over time using linear mixed models, with treatment strategy (arms 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 (SPSS Inc., Chicago, IL).

RESULTS

Study profile

In total 610 patients were included, 479 (79%) with RA and 122 (20%) with UA; nine patients could not be classified because of missing values. Over the year 23 patients withdrew consent, three discontinued because of a revised diagnosis and six because of comorbidity. 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%) patients with RA and 79/122 (65%) patients with UA were in early remission (12 patients were lost to follow-up and five were not classifiable because of missing data). A total of 144/387 (37%) (114/291 (39%) with RA and 28/79 (35%) with UA, two had missing data) also fulfilled the proposed ACR/EULAR remission definition.

In total, 161/610 (26%) patients not in DAS remission were randomised, 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 OP group. Thirty-three of these patients tapered prednisone and for 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 antibody (ACPA)-positive and had a shorter symptom duration than randomised patients.[8] Clinical characteristics at baseline and 4 months were comparable in arms 1 and 2 (table 1). After 4 months 12 patients were lost to follow-up and 598 patients were categorised a described in this table.

Outcomes after 1 year

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

After 1 year, mean HAQ and DAS were lower in the group with early DAS remission than in arms 1 and 2. Over time, no significant difference in DAS and HAQ between arms 1 and 2 was found (mean DAS difference of 0.03 95% CI -0.16 to 0.22, mean HAQ difference 0.04, 95% CI 0.01 to 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 Joint 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, n (%)	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, n (%)	247 (64)	59 (71)	49 (63)	28 (56)
RF positive, n (%)	224 (58)	41 (49)	43 (55)	23 (46)
ACPA positive, n (%)	225 (58)	40 (48)	37 (47)	25 (50)
RA(2010), n (%)	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, n (%)	63 (16)	10 (12)	13 (17)	3 (6)
Follow-up – 4 months				
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
Follow up – 1 year				
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, n (%)	65 (17)	12 (15)	12 (16)	2 (4)
DAS-Remission, n (%)	263 (68)	21 (25)	32 (41)*	12 (24)
Drug free remission, n (%)	124 (32)	1 (1)	0 (0)	5 (10)
ACR/EULAR remission, n (%)	122 (32)	9 (11)	13 (17)	4 (8)
SHS progression, median (IQR)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)

After 4 months 12 patients were lost to follow up and 598 patients were categorized a described in this table. SD: standard deviation, IQR: interquartile ranges, n: number, DAS: disease activity score, HAQ: Health Assessment Questionnaire, RF: rheumatoid factor, ACPA: anti-citrullinated protein antibody, RA(2010): rheumatoid arthritis according to the 2010 classification criteria, VAS: visual analogue scale, ESR: erythrocyte sedimentation rate, SHS: Sharp- van de Heijde Score, Progression: increase in SHS ≥0.5 points, DAS-remission: DAS<1.6[12], 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 [13]. Erosive denotes the presence of at least 1 erosion on radiographs of hands and feet. *p-value <0.05 between arm 1 and arm 2.

Median (IQR) SHS progression score in all groups was 0 (0–0), with no difference between patients with UA and those with RA. 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 one patient, 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 whom, 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%) patients re-treated according to protocol and 22/40 (55%) 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 ADA and in 19 patients other steps were taken (one patient had missing data). In arm 2, 26 patients tapered to monotherapy, 28 increased ADA and in 21 patients other steps were taken (three patients had missing data). More patients in arm 2 who increased ADA achieved DAS remission after 1 year, than patients in arm 1 who switched to ADA (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 with 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), included more women (85/96 (89%) versus 291/462 (63%), p<0.001) and fewer were ACPA-positive (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 two deaths and 14 other serious adverse events (SAE) in 14 patients.[8]

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,

Table 2. Number of adverse events reported between 4 months and 1 year for patients in the early 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	-	-
Dizzyness	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

AE: adverse event. *One or more adverse events possible per patient.

nausea, upper airway and skin/mucosa infections and skin rashes (table 2). In 26/610 (4%) patients, SAE were reported. Three patients died: one of a squamous cell carcinoma of the tongue (early remission group), one of a cerebral tumour (arm 2, treated with ADA 40 mg/2 weeks for 4 months) and one patient of an ovarian carcinoma (OP group; in the 7 months before 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 (4%) patients, 10 in the early remission group, seven in arm 1, six in arm 2 and two in the OP group. Reasons for admission to hospital were complications of malignancy (the three patients, described above), pneumonia (four patients; two in arm 1, one in arm 2 and one in the OP group), suspicion of septic arthritis (arm 1, cultures remained negative), cellulitis of the lower leg (two patients; early remission group and arm 1), percutaneous coronary intervention for cardiac ischaemia (two patients; early remission group and arm 2), cardiac arrhythmia (two 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), femoral head necrosis (arm 2) and trauma due to a car accident (arm 1).

DISCUSSION

In patients with early arthritis, remission defined by Disease Activity Score can be achieved in 54% after 1 year with initial treatment with MTX and a tapered high dose of prednisone followed by remission-steered adjustments to treatment. 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 RA, 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 ADA resulted in more remission (41% versus 25%) than treatment expansion with SSZ and HCQ, reserving ADA as possible next step. Functional ability, radiological damage progression and toxicity were similar.

This study is the first to steer according to 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 have reported similar percentages, and in those studies treatment was continued for 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] Perhaps 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 might 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 which has been proved to be better than DMARD monotherapy in patients with RA[6,24,25]- followed after randomisation by progressive treatments either with multiple DMARDs or with a TNF inhibitor, which proved to be effective both in early and established RA.[26-28]

We used the DAS criteria to define remission. These criteria are less stringent than the provisional remission criteria proposed by ACR and EULAR. Nonetheless, we have shown that our patients in DAS remission have good functional ability and virtually no progression of damage.

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 fewer patients achieving remission after switching from poly-DMARDs and prednisone to ADA (both in arm 1). This suggests that if remission is not achieved with initial combination therapy, it is better to introduce ADA early. It appears that patients for whom prednisone and poly-DMARDs fail, may respond less well to any other treatment, as was previously shown 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 SAE (infections, cardiovascular disease, femoral head necrosis, diabetic complications) might be related to the use of prednisone. Thirty-six per cent of our patients did not achieve DAS remission with the initial treatment, and 16% did not achieve DAS remission with any treatment. Other (biological) treatments 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 blinded to treatment. In some cases the patients refused to take the next treatment step. Despite the protocol deviations that ensued, in general, treatment remained steered according to 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, most patients with early RA 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 with the initial treatment and start tapering medication, 68% are in remission and 32% are in DFR after 1 year. For patients not in early remission, combination therapy including ADA 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, RA may not progress to the chronic and destructive autoimmune disease as we knew it.

REFERENCE LIST

1. Mottonen T, Hannonen P, Leirisalo-Repo M et al. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. Lancet 1999;353(9164):1568-1573.
2. Welsing PM, van Gestel AM, Swinkels HL, Kiemeney LA, van Riel PL. The relationship between disease activity, joint destruction, and functional capacity over the course of rheumatoid arthritis. Arthritis Rheum 2001;44(9):2009-2017.
3. Welsing PM, Landewe RB, van Riel PL et al. The relationship between disease activity and radiologic progression in patients with rheumatoid arthritis: a longitudinal analysis. Arthritis Rheum 2004;50(7):2082-2093.
4. Klareskog L, van der Heijde D, de Jager JP et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet 2004;363(9410):675-681.
5. Lipsky PE, van der Heijde DM, St Clair EW et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. N Engl J Med 2000;343(22):1594-1602.
6. Boers M, Verhoeven AC, Markusse HM et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet 1997;350(9074):309-318.
7. Verpoort KN, van Dongen H, Allaart CF, Toes RE, Breedveld FC, Huizinga TW. Undifferentiated arthritis--disease course assessed in several inception cohorts. Clin Exp Rheumatol 2004;22(5 Suppl 35):S12-S17.
8. Wevers-de Boer K, Visser K, Heimans L et al. Remission induction therapy with methotrexate and prednisone in patients with early rheumatoid and undifferentiated arthritis (the IMPROVED study). Ann Rheum Dis 2012;71(9):1472-1477.
9. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): A randomized, controlled trial. Arthritis Rheum 2008;58(2 Suppl):S126-S135.
10. Aletaha D, Neogi T, Silman AJ et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010;69(9):1580-1588.
11. van Dongen H, van Aken J, Lard LR et al. Efficacy of methotrexate treatment in patients with probable rheumatoid arthritis: a double-blind, randomized, placebo-controlled trial. Arthritis Rheum 2007;56(5):1424-1432.
12. Prevoo ML, van Gestel AM, van 't Hof, van Rijswijk MH, van de Putte LB, van Riel PL. Remission in a prospective study of patients with rheumatoid arthritis. American Rheumatism Association preliminary remission criteria in relation to the disease activity score. Br J Rheumatol 1996;35(11):1101-1105.
13. Felson DT, Smolen JS, Wells G et al. American College of Rheumatology/European League against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Ann Rheum Dis 2011;70(3):404-413.
14. Siegert CE, Vleming LJ, Vandenbroucke JP, Cats A. Measurement of disability in Dutch rheumatoid arthritis patients. Clin Rheumatol 1984;3(3):305-309.
15. van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. J Rheumatol 2000;27(1):261-263.
16. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. Psychol Bull 1979;86(2):420-428.
17. Breedveld FC, Weisman MH, Kavanaugh AF et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive

rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum 2006;54(1):26-37.

18. Grigor C, Capell H, Stirling A et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. Lancet 2004;364(9430):263-269.
19. Makinen H, Kautiainen H, Hannonen P et al. Sustained remission and reduced radiographic progression with combination disease modifying antirheumatic drugs in early rheumatoid arthritis. J Rheumatol 2007;34(2):316-321.
20. van der Heijde D, Klareskog L, Rodriguez-Valverde V et al. Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. Arthritis Rheum 2006;54(4):1063-1074.
21. Willemze A, van der Linden MP, le Cessie S et al. The window of opportunity in ACPA-positive rheumatoid arthritis is not explained by ACPA characteristics. Ann Rheum Dis 2011;70(9):1697-1698.
22. Zeidler H. The need to better classify and diagnose early and very early rheumatoid arthritis. J Rheumatol 2012;39(2):212-217.
23. Keystone E, Freundlich B, Schiff M, Li J, Hooper M. Patients with moderate rheumatoid arthritis (RA) achieve better disease activity states with etanercept treatment than patients with severe RA. J Rheumatol 2009;36(3):522-531.
24. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF et al. Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial. Ann Intern Med 2007;146(6):406-415.
25. Klarenbeek NB, Guler-Yuksel M, van der Kooij SM et al. The impact of four dynamic, goal-steered treatment strategies on the 5-year outcomes of rheumatoid arthritis patients in the BeSt study. Ann Rheum Dis 2011;70(6):1039-1046.
26. de Jong PH, Hazes JM, Barendregt PJ et al. Induction therapy with a combination of DMARDs is better than methotrexate monotherapy: first results of the tREACH trial. Ann Rheum Dis 2012.
27. Wiens A, Venson R, Correr CJ, Otuki MF, Pontarolo R. Meta-analysis of the efficacy and safety of adalimumab, etanercept, and infliximab for the treatment of rheumatoid arthritis. Pharmacotherapy 2010;30(4):339-353.
28. Navarro-Sarabia F, Ariza-Ariza R, Hernandez-Cruz B, Villanueva I. Adalimumab for treating rheumatoid arthritis. Cochrane Database Syst Rev 2005;(3):CD005113.
29. van der Kooij SM, le Cessie S, Goekoop-Ruiterman YP et al. Clinical and radiological efficacy of initial vs delayed treatment with infliximab plus methotrexate in patients with early rheumatoid arthritis. Ann Rheum Dis 2009;68(7):1153-1158.

CHAPTER 5

OUTCOMES OF TWO YEARS REMISSION STEERED TREATMENT IN EARLY ARTHRITIS PATIENTS – THE IMPROVED-STUDY

Submitted

L. Heimans, K.V.C. Wevers-de Boer, G. Akdemir,
Y.P. Goekoop-Ruiterman, E.T. Molenaar, J.B. Harbers,
A.J. Peeters, G.M. Steup-Beekman, L.R. Lard, M.P.D.M. de Buck,
P.B.J. de Sonnaville, B.A.M. Grillet, T.W.J. Huizinga, C.F. Allaart

ABSTRACT

Background: To assess 2-year clinical and radiological outcomes of remission steered treatment in patients with early arthritis.

Methods: 610 patients with early rheumatoid arthritis (RA) or undifferentiated arthritis (UA) were treated with methotrexate (MTX) and tapered high dose of prednisone. Patients in early remission (disease activity score (DAS44<1.6) after 4 months tapered and stopped medication. Patients who did not achieve early DAS-remission were randomized to either MTX, hydroxychloroquine, sulphasalazine and low dose prednisone (arm 1) or to MTX and adalimumab (arm 2). During follow-up, medication was increased, switched or restarted in case of no remission and tapered and stopped in case of remission. Proportions of (drug free) remission (DFR) were analyzed separately for the treatment strategies and patients with RA and UA.

Results: After 2 years, 301/610 (49%) of the patients were in DAS-remission and 131/610 (21%) in DFR. In the early remission group 241/387 patients (62%) achieved DAS-remission and 111/387 (29%) DFR. In arm 1 22/83 (27%) achieved remission and 7/83 (8%) DRF. In arm 2 24/78 (31%) achieved remission and 7/78 (9%) DFR. Patients with RA and with UA achieved DAS-remission in comparable percentages (RA: 234/479 (49%), UA: 64/122 (52%), p=0.25). UA patients more often achieved DFR (42/122 (34%)) than RA patients (88/479 (18%), p<0.001). Median (IQR) radiological progression in all groups was 0 (0-0).

Conclusions: After 2 years remission steered treatment, patients in the early remission group more often achieved (drug) free remission than patients who needed additional treatment steps in the randomization arms. Radiologic damage progression remained well suppressed.

INTRODUCTION

In rheumatoid and undifferentiated arthritis (RA and UA) it is preferable to initiate treatment early after onset of symptoms to induce early remission and maybe reverse the disease process.[1-3]

In the IMPROVED-study we have shown that it is possible for 61% of the RA patients and 65% of the UA patients to achieve early remission (Disease Activity Score DAS<1.6) after 4 months treatment with methotrexate (MTX) and tapered high dose of prednisone.[4] In case of early remission, medication was tapered until drug free remission (DFR) was achieved. Those patients who did not achieve early remission were randomized. In all patients, treatment adjustments, including drug tapering, were made every 4 months aiming at a DAS<1.6. Here, the clinical and radiological outcomes after 2 year follow-up are presented.

METHODS

Study design and patients

The IMPROVED-study (ISRCTN Register number 11916566 and EudraCT number 2006-006186-16) is a multicenter, 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. The study protocol was approved by the Medical Ethics Committee of each participating center, all patients gave written informed consent.

Patients were ≥18 years, with recent onset RA or UA, a DAS≥1.6 and no previous antirheumatic therapy. RA was defined as fulfilling the 2010 the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) classification criteria [5] with a symptom duration ≤2 years. UA was defined as at least one joint with clinical synovitis and one other painful joint, clinically suspected for early RA, regardless of symptom duration. Exclusion criteria were published previously.[4, 6]

Intervention

All patients started with 4 months of MTX 25 mg/week and prednisone 60 mg/day which was tapered to 7.5 mg/day in 7 weeks. Every 4 months the DAS was assessed by a trained research nurse, blinded for treatment allocation. The treatment target of the study was a DAS<1.6 which was considered to denote remission (figure 1).[7]

Patients in early remission after 4 months tapered prednisone to 0. When still in remission after 8 months, MTX was also tapered to 0. In case of a DAS≥1.6 after 8 months, prednisone was restarted at 7.5 mg/day.

Patients with a DAS≥1.6 after 4 months were randomized, either hydroxychloroquine (HCQ) 400mg/day and sulphasalazine (SSZ) 2000mg/day were added to MTX and prednisone (arm 1) or they switched to MTX 25mg/week plus adalimumab (ADA) 40mg/2weeks (arm 2). Patients who had achieved early remission and discontinued prednisone, then lost

remission and restarted prednisone without achieving remission, were also randomized ('delayed randomization') (figure 1). In arm 1, if remission after 8 months was achieved, prednisone, SSZ and then HCQ were stopped. MTX was stopped if remission remained 4 months later. If remission was not achieved at 8 months, patients switched to MTX+ADA (40mg/2weeks, increased to 40 mg/week if DAS remained ≥1.6). Patients in arm 2 tapered ADA in case of remission after 8 months and increased ADA to 40mg/week in case of no remission. In both arms, if patients did not achieve remission on a combination of MTX+ADA 40mg/week, further treatment decisions were left to the opinion of the rheumatologist (figure 1). A detailed description of the randomization procedure was published previously.[6]

Primary and secondary outcomes

Primary outcomes were percentages of patients in remission and DFR based on a DAS<1.6 or on the proposed remission definition published by the ACR/EULAR in 2011.[8]

Secondary outcomes were mean DAS, mean functional ability as measured by the Dutch version of the Health Assessment Questionnaire (HAQ [9]), toxicity and radiological damage progression of the joints in hands and feet (defined as an increase of ≥0.5 point in Sharp-van der Heijde score (SHS) [10]).

Baseline and yearly radiographs of hands and feet were blinded for patient identity and scored in time random order for the presence of erosions and joint space narrowing by 2

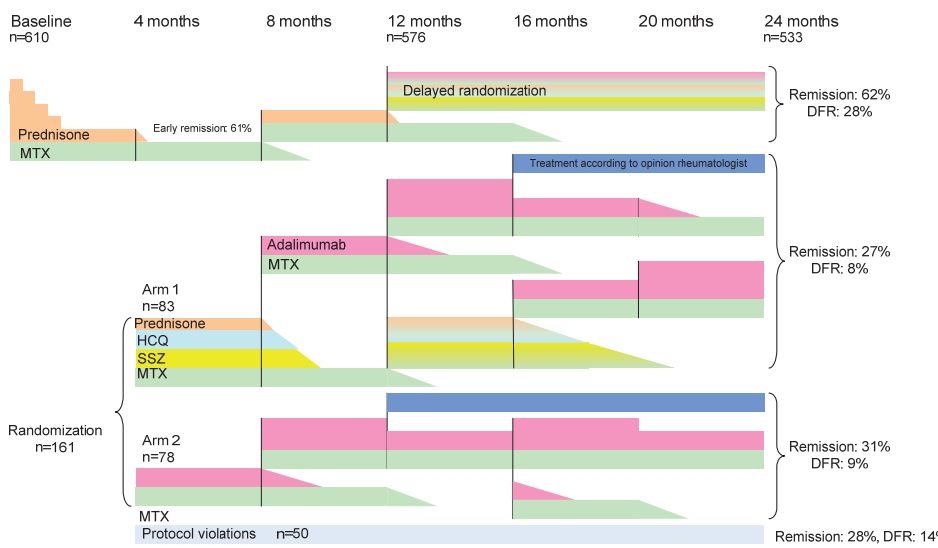

Figure 1. Study flow chart with percentages DAS- and drug free remission after the second study year. DFR: drug free remission, MTX: methotrexate, HCQ: hydroxychloroquine, SSZ: sulfasalazine. Colours: orange=prednisone, green=MTX, dark blue=treatment left to decision of rheumatologist, aqua=HCQ, yellow=SSZ, purple=adalimumab biweekly, double thickness purple=adalimumab weekly, grey=protocol not followed as required but remained in follow up.

trained, independent readers (LH and GA). Only 8% of the patients showed progression and therefore intra-class correlation coefficients were not suitable for measuring reliability.[11] In 443 of 496 patients who had radiographs taken after 2 years follow-up, there was an inter-reader difference of <2 between the progression scores of both readers. For the other 53 a consensus score was reached.

Outcomes were reported separately for patients who achieved early DAS-remission and those randomized and were compared between the randomization arms, as well as between patients with RA and patients with UA and between patients in or not in remission after 2 years.

Statistical analysis

We performed intention-to-treat analyses. Outcomes were analyzed using students *t*-tests, Mann Whitney U tests and χ^2 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. All statistical analyses were conducted with SPSS for Windows version 20.0 (SPSS Inc., Chicago, IL).

RESULTS

Study population

Of the 610 patients included in the IMPROVED-study, 479 (79%) had classifiable RA and 122 (20%) UA (9 patients could not be classified because of missing data). During the first 2 years 79 patients were lost to follow-up; 54 withdrew consent, 9 discontinued because of a revised diagnosis and 8 because of co-morbidity. Eight patients died,[4, 6] 3 of those in the second year of the study (supplementary table S1).

Of 610 patients, 387 (63%) achieved early remission, 375 (61%) at 4 months, 12 (2%) more after a reassessment 4-6 weeks later (if the rheumatologists disagreed with the DAS after 4 months). One-hundred-sixty-one of 610 patients (26%) were randomized; 83 patients into arm 1 and 78 to arm 2. Fifty patients with a DAS≥1.6 after 4 months were not randomized as the protocol required and were analyzed in the outside of protocol (OP) group. Twelve patients left the study before the assessment at 4 months (table 1).

Remission and drug free remission

In 50/610 patients (8%) remission had never been achieved during 2 years follow-up. Most patients at least once achieved remission which was lost again and medication was reintroduced. At the next evaluation, remission had been achieved again in >70% of those patients. Fifty-five patients (9%) (37 with RA, 17 with UA, p=0.01. One patient was unclassifiable because of missing data) were in sustained remission from 4 months through to 2 years (and therefore in DFR from 8 months to 2 years). After 2 years follow up, 301/610 (49%) patients were in remission and 131/610 (21%) were in DFR. In the early remission group, 241/387 (62%) were in remission and 111/387 (29%) in DFR after

Table 1. Baseline characteristics of the IMPROVED study population.

	Early remission n = 387	Arm 1 n = 83	Arm 2 n = 78	OP 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
Age in years, mean ± SD	52±14	49±14	51±14	54±14
Female, n (%)	240 (62)	64 (77)	58 (74)	42 (84)
Symptom duration (weeks), median (IQR)	17 (9-30)	22 (9-41)	21 (8-31)	18 (9-42)
RF positive, n (%)	224 (58)	41 (49)	43 (55)	23 (46)
ACPA positive, n (%)	225 (58)	40 (48)	37 (47)	25 (50)
RA(2010), n (%)	298 (77)	66 (80)	66 (85)	40 (80)
Swollen Joint Count, median (IQR)	5 (2-9)	6 (3-10)	8 (4-12)	7 (3-13)
Tender Joint Count, median (IQR)	5 (3-8)	8 (6-13)	9 (6-13)	8 (6-14)
ESR mm/hr, median (IQR)	23 (8-38)	28 (13-41)	22 (11-41)	29 (16-42)
VAS global health in mm, mean ± SD	43 ± 24	53 ± 20	54 ± 22	49 ± 23
Total SHS, median (IQR)	0 (0-0.5)	0 (0-0)	0 (0-0)	0 (0-0)
Erosive, n (%)	63 (16)	10 (12)	13 (17)	3 (6)

After 4 months 12 patients were lost to follow up and 598 patients were categorized as described in this table. OP outside of protocol, SD: standard deviation, IQR: interquartile ranges, n: number, DAS: disease activity score, HAQ: Health Assessment Questionnaire, RF: rheumatoid factor, ACPA: anti-citrullinated protein antibody, RA(2010): rheumatoid arthritis according to the 2010 classification criteria, ESR: erythrocyte sedimentation rate, VAS: visual analogue scale, SHS: Sharp- van de Heijde Score, Erosive: at least 1 erosion. Arm 1: randomized at 4 months to methotrexate, sulphasalazine, hydroxychloroquine and low dose prednisone. Arm 2: randomized at 4 months to methotrexate and adalimumab.

2 years. In arm 1, 22/83 (27%) were in remission compared to 24/78 (31%) in arm 2 (p=0.76). DFR was achieved by 7/83 patients in arm 1 (8%) and in 7/78 patients in arm 2 (9%) (p=0.90). Remission defined according to the proposed ACR/EULAR remission criteria was achieved in 138/610 (23%) patients; 117/387 (30%) in the early remission group, 2/83 (2%) in arm 1 and 14/78 (18%) in arm 2 (arm 1 versus arm 2: p=0.001).

After 2 years, comparable percentages of ACPA positive and ACPA negative patients were in remission (ACPA positive: 172/333 (52%), ACPA negative: 125/262 (48%), p=0.68) but more ACPA negative patients achieved DFR than ACPA positive patients: 74/262 (28%) versus 54/333 (16%), p<0.001. Comparable percentages of patients with UA or with RA achieved remission after 2 years (UA: 64/122 (52%) and RA: 234/479 (49%), p=0.25) but significantly more patients with UA, of whom 94% were ACPA-negative, achieved DFR (41/122 (34%) compared to 89/479 (19%) in RA patients, p<0.001).

Patients who were not in remission at 2 years, had a higher tender joint count than patients who were in remission (median (IQR) 4 (2-6) versus 0 (0-1) p<0.001) and also higher scores on the visual analogue scale (VAS) for pain (mean (SD) 41 (24) versus 11 (16) p<0.001), higher ESR (13 (9-22) versus 6 (3-13) p<0.001) and a higher swollen joint count (1 (0-3) versus 0 (0-0), p<0.001). Except for ESR and swollen joint count, the statistical significant differences between these patients were already present at baseline.

Remission rates were comparable between patients who at baseline had <12 weeks symptom duration and patients who had symptoms for ≥12 weeks, 106/204 (52%) versus 192/397 (50%) (p=0.31), as were DFR rates 50/204 (25%) versus 80/397 (20%) (p=0.19).

DAS and HAQ after 2 years

At 2 years, mean (SD) DAS was 1.25 (0.77) in the early remission group, 2.02 (0.70) in arm 1 and 1.92 (0.85) in arm 2 (arm 1 versus arm 2: p=0.45). Patients treated outside the protocol had a mean DAS of 1.9 (0.7) (table 2). Mean (SD) HAQ at 2 years was 0.38 (0.48) in the early remission group, 0.90 (0.66) in arm 1 and 0.83 (0.67) in arm 2 (arm 1 versus arm 2: p=0.55) (table 2). Compared to baseline, in all groups improvement in mean HAQ was >0.20 and therefore clinically relevant.[9] Mean (SD) HAQ in patients who were in remission at 2 years was 0.29 (0.39) compared to 0.94 (0.63) in patients who were not in remission (p<0.001). Mean (SD) HAQ at 2 years of patients in ACR/EULAR remission was 0.14 (0.28).

Over time, DAS or HAQ were not significantly different between arm 1 and 2 (mean difference (95%CI) LMM for DAS 0.01 (-0.2;0.2) and for HAQ 0.1 (-0.1;0.2)).

Radiological joint damage

Of the total study population, 50/610 (8%) patients showed radiological progression defined as an increase in SHS of ≥0.5; in the early remission group 33/387 (9%) patients showed progression, in arm 1 9/83 (11%), in arm 2 5/78 (6%) (arm 1 versus arm 2: p=0.31) and in the OP-group 3/50 (6%). Median SHS progression in all groups was 0 (range 0-22). There was no significant difference in progression scores between patients who at 2 years were in DAS-remission and patients who were not. Eight patients (1%) after 2 years had radiological damage progression of ≥5 points which represents the minimal clinically important difference.[12] Seven of these 8 patients had achieved early remission and one patient was in persistent remission from 4 months.

Compared to the results after 1 year we found less erosions after 2 years, probably due to differences in interpretation of the minimal changes on radiographs. The differences were found across the scores of both readers, one of whom had also scored year 1 while the new reader used the same scoring method and had received the same training. In the early remission group 39/387 (10%) showed erosions after 2 years compared to 65 (17%) after year 1, in arm 1 2/83 (2%) after 2 years compared to 12 (15%) after year 1, in arm 2 8/10 (6%) after 2 years and 12 (16%) after year 1 and in the OP-group 1/50 (2%) after 2 years and 2 (4%) after year 1.

Therapy

Of the 400 patients not in DFR at 2 years, 196 patients were on DMARD monotherapy, 12 used a combination of multiple non-biologic DMARDs, 37 a combination of non-biologic DMARDs with prednisone, 79 with adalimumab and 18 with another biologic

Table 2. Outcomes in the IMPROVED-study population after 2 years.

	Early remission n = 387	Arm 1 n = 83	Arm 2 n = 78	p arm 1 vs 2	OP group n = 50
DAS, mean ± SD	1.3 ± 0.8	2.0 ± 0.7	1.9 ± 0.9	0.45	1.9 ± 0.7
HAQ, mean ± SD	0.4 ± 0.5	0.9 ± 0.7	0.8 ± 0.7	0.55	0.8 ± 0.7
Swollen Joint Count, median (IQR)	0 (0-1)	1 (0-2)	0 (0-2)	0.25	0 (0-2)
Tender Joint Count, median (IQR)	0 (0-2)	3 (2-5)	3 (1-6)	0.84	2 (1-4)
ESR mm/hr, median (IQR)	8 (4-16)	11 (6-20)	9 (6-17)	0.19	14 (7-25)
VAS global health in mm, mean ± SD	18 ± 21	30 ± 21	28 ± 24	0.61	32 ± 22
Total SHS, median (IQR)	0 (0-0.5)	0 (0-1.1)	0 (0-0)	0.12	0 (0-0.3)
Erosive, n (%)	39 (10)	2 (2)	8 (10)	0.04	1 (2)
SHS progression, n (%)	33 (9)	9 (11)	5 (6)	0.31	3 (6)
DAS-remission, n (%)	241 (62)	22 (27)	24 (31)	0.76	15 (28)
Drug free remission, n (%)	111 (28)	6 (7)	7 (9)	0.73	7 (14)
ACR/EULAR remission, n (%)	117 (30)	2 (2)	14 (18)	0.001	5 (10)

After 4 months 12 patients were lost to follow up and 598 patients were categorized.
OP: outside of protocol, SD: standard deviation, IQR: interquartile ranges, n: number, DAS: disease activity score, HAQ: Health Assessment Questionnaire, ESR: erythrocyte sedimentation rate, VAS: visual analogue scale, SHS: Sharp- van de Heijde Score, Erosive: at least 1 erosion, Progression: increase in SHS ≥0.5 points, DAS-remission: DAS<1.6[7], 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 [13].
Arm 1: randomized after 4 months to methotrexate, sulphasalazine, hydroxychloroquine and low dose prednisone. Arm 2: randomized after 4 months to methotrexate and adalimumab.

agent. In 16 patients therapy at 2 years was unknown because of missing data and 42 patients were drug free but not in remission.

During 2 years follow-up, 43/83 (52%) of the patients in arm 1 switched to ADA+MTX and after 2 years 28 patients still used ADA+MTX.

Toxicity

During the second year of the study, 337/610 (55%) patients reported 704 adverse events (AE): 53% of the patients in the early remission group, 64% in arm 1, 67% in arm 2 (arm 1 versus arm 2: p=0.71) and 54% in the OP-group. The most common AE were gastro-intestinal complaints, upper airway infections and skin rashes (table 3). Twenty-five serious adverse events (SAE) were reported in the early remission group, 5 in arm 1, 8 in arm 2 and 3 in the OP group (table S1).

DISCUSSION

Two years after initial therapy with MTX and a tapered high dose of prednisone, followed by remission steered treatment including drug tapering and discontinuation, 49% of the patients with early RA or UA were in remission and 21% were in DFR. Patients

Table 3. Number of adverse events reported between 1 year and 2 years.

	Early remission n=387	Arm 1 n=83	Arm 2 n=78	Outside protocol n=50
Patients with AE, no (%)	205/387 (53%)	53/83 (64%)	52/78 (67%)	27/50 (54%)
Total number of AE	408	129	109	58
Cardiovascular	25	5	8	4
Pulmonary	17	5	2	2
Gastrointestinal	67	16	14	12
GI complaints	8	2	2	-
Nausea/emesis	23	2	4	4
Increased liver enzymes	15	7	3	4
Other	21	5	5	4
Neuro-psychiatric	37	5	7	3
Headache	14	-	4	1
Dizziness	7	1	-	1
Mood disorders	4	-	-	1
Other	12	4	3	-
Urogenital	7	3	2	3
Skin/mucous membranes	45	18	15	3
Rash	19	8	5	-
Hair loss/thinning	4	1	1	1
Sicca complaints	3	-	-	1
Eczema	3	1	-	-
Other	16	8	9	1
Infections	106	38	41	18
Upper airway tract	29	11	16	10
Gastro-intestinal	4	1	-	2
Skin/mucosa	14	2	4	2
Pneumonia/bronchitis	9	1	1	1
Urinary tract	15	7	5	1
Flu/unspecified fever	25	10	6	1
Other	10	6	9	1
Trauma/injury	13	5	2	3
Infusion reaction	3	1	-	-
Malaise	9	5	1	1
Surgical procedures without hospitalization	13	5	4	1
Other	65	23	12	8

AE: adverse event. *One or more adverse events possible per patient.

who achieved early remission after 4 months more often achieved remission (62%) and DFR (29%) at 2 years than patients who did not (29% remission and 9% DFR, without differences between the two treatment strategies). Radiological damage progression was seen in only 8% of the patients and functional ability improved up to the normal range in those who achieved remission.

The radiological results are better than previously reported in patients with early RA.[14-17] For example, 7-33% of the patients in the BeSt study showed progression after 1 year and 20-47% of the patients in the NEO-RACo study showed progression after 2 years.[14, 18] Still, the overall remission rates in the IMPROVED-study are only slightly higher than what we observed in the BeSt study.[14, 19] At baseline, those patients had active RA (1987 criteria[20]) with high disease activity, were more often ACPA positive patients and had longer symptom duration.

Furthermore, only half of the BeSt study population received initial combination therapy and the target of treatment was low disease activity (DAS≤2.4) instead of remission (DAS<1.6). That only half of the patients achieved remission in the IMPROVED-study may in part be explained by rapid tapering and discontinuation of drugs as soon as DAS<1.6 was achieved. There were only 55 patients who had been in remission from 4 months onwards. Together with the exception of 50 patients who never achieved remission, all others had achieved but lost remission at least once. It is possible that steering at a treatment target of remission defined by DAS<1.6 is hampered by some patients reporting pain and joint tenderness where no joint swelling was found. One may argue that using DAS<1.6 as the treatment target is unrealistic, as with a DAS just above the threshold of 1.6 inflammation is equally well suppressed, resulting in equally well prevented joint damage. Still, patients not in remission had a mean HAQ approaching 1 whereas patients in remission had near-normal functional ability. This, however, may have come at the cost of relatively high usage of medications with potential side effects and high costs.

We found the highest remission and DFR rates in patients who had achieved early remission. It may be that patients who fail to achieve remission on initial combination treatment are a selected group with less responsive disease. After 1 year follow-up we have reported there was a statistically significant difference in remission rates between the randomization arms.[6] After 2 years, the remission rates were comparable and this is probably due to remission steered treatment adjustments in both arms and due to treatment overlap in the treatment strategies during follow-up.

Remission rates were comparable between patients with RA and UA. This could either indicate that we missed the 'window of opportunity' and therefore the opportunity to alter the disease course. However, the outcomes between patients with <12 weeks symptom duration and those with ≥12 weeks symptom duration are comparable. It could also indicate that early RA and UA, when effectively treated, result in comparable outcomes. On the other hand, UA patients more often achieved DFR than RA patients. This may suggest that, although it is possible to achieve remission in RA and UA in comparable percentages, the possibility to taper and stop medication when remission is achieved, is not. These same arguments probably also explain the higher DFR rates in ACPA negative patients, compared to ACPA positive patients.

We found less erosive joint damage after 2 years than after 1 year. Our data suggest that this is not due to repair, which has been shown to occur more often in damaged joints.[21] Joint damage, in general, was minimal and therefore normal variations were difficult to distinguish

from early abnormalities. Furthermore, the radiographs taken at baseline, after 1 year and after 2 years, were scored in random order. It has been demonstrated that chronological scoring is more sensitive to change and may lead to an increased detection of clinically relevant progression.[22, 23] Since the overall progression rates are so low and for most patients below the minimal clinically important difference, it is unlikely that the small difference between the erosion scores after 1 and 2 years affect the main radiological outcomes.

In conclusion, in patients with recent onset RA or UA, 2 years of remission targeted treatment results in 49% of the patients being in remission and 21% in DFR and virtually no radiological damage progression. Patients who achieved early remission also achieved more remission and DFR after 2 years than the patients who had not achieved early remission and were randomized to 2 treatment strategies, between which no differences in outcomes were found. These results suggest that initial treatment with MTX and prednisone followed by remission steered treatment is effective in suppressing disease activity and in particular in suppressing joint damage progression.

REFERENCE LIST

1. van Tuyl LH, Lems WF, Voskuyl AE et al. Tight control and intensified COBRA combination treatment in early rheumatoid arthritis: 90% remission in a pilot trial. Ann Rheum Dis 2008;67(11):1574-1577.
2. Puolakka K, Kautiainen H, Mottonen T et al. Early suppression of disease activity is essential for maintenance of work capacity in patients with recent-onset rheumatoid arthritis: five-year experience from the FIN-RACo trial. Arthritis Rheum 2005;52(1):36-41.
3. Grigor C, Capell H, Stirling A et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. Lancet 2004;364(9430):263-269.
4. Wevers-de Boer K, Visser K, Heimans L et al. Remission induction therapy with methotrexate and prednisone in patients with early rheumatoid and undifferentiated arthritis (the IMPROVED study). Ann Rheum Dis 2012;71(9):1472-1477.
5. Aletaha D, Neogi T, Silman AJ et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010;69(9):1580-1588.
6. Heimans L, Wevers-de Boer KV, Visser K et al. A two-step treatment strategy trial in patients with early arthritis aimed at achieving remission: the IMPROVED study. Ann Rheum Dis 2013.
7. Prevoo ML, van Gestel AM, van 't Hof M, van Rijswijk MH, van de Putte LB, van Riel PL. Remission in a prospective study of patients with rheumatoid arthritis. American Rheumatism Association preliminary remission criteria in relation to the disease activity score. Br J Rheumatol 1996;35(11):1101-1105.
8. Felson DT, Smolen JS, Wells G et al. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Arthritis Rheum 2011;63(3):573-586.
9. Siegert CE, Vleming LJ, Vandenbroucke JP, Cats A. Measurement of disability in Dutch rheumatoid arthritis patients. Clin Rheumatol 1984;3(3):305-309.
10. van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. J Rheumatol 1999;26(3):743-745.
11. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. Psychol Bull 1979;86(2):420-428.
12. Bruynesteyn K, van der Heijde D, Boers M et al. Determination of the minimal clinically important difference in rheumatoid arthritis joint damage of the Sharp/van der Heijde and Larsen/Scott scoring methods by clinical experts and comparison with the smallest detectable difference. Arthritis Rheum 2002;46(4):913-920.
13. Felson DT, Smolen JS, Wells G et al. American College of Rheumatology/European League

against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Ann Rheum Dis 2011;70(3):404-413.

14. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. Arthritis Rheum 2005;52(11):3381-3390.
15. Breedveld FC, Weisman MH, Kavanaugh AF et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum 2006;54(1):26-37.
16. Bakker MF, Jacobs JW, Welsing PM et al. Low-dose prednisone inclusion in a methotrexate-based, tight control strategy for early rheumatoid arthritis: a randomized trial. Ann Intern Med 2012 Mar 6;156(5):329-39.
17. O'Dell JR, Mikuls TR, Taylor TH et al. Therapies for active rheumatoid arthritis after methotrexate failure. N Engl J Med 2013 Jul 25;369(4):307-18.
18. Leirisalo-Repo M, Kautiainen H, Laasonen L et al. Infliximab for 6 months added on combination therapy in early rheumatoid arthritis: 2-year results from an investigator-initiated, randomised, double-blind, placebo-controlled study (the NEO-RACo Study). Ann Rheum Dis 2013 Jun;72(6):851-7.
19. Klarenbeek NB, Guler-Yuksel M, van der Kooij SM et al. The impact of four dynamic, goal-steered treatment strategies on the 5-year outcomes of rheumatoid arthritis patients in the BeSt study. Ann Rheum Dis 2011;70(6):1039-1046.
20. Arnett FC, Edworthy SM, Bloch DA et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31(3):315-324.
21. van der Linden MP, Boja R, Klarenbeek NB, Huizinga TW, van der Heijde DM, van der Helm-van Mil AH. Repair of joint erosions in rheumatoid arthritis: prevalence and patient characteristics in a large inception cohort. Ann Rheum Dis 2010 Apr;69(4):727-9.
22. Bruynesteyn K, van der Heijde D, Boers M et al. Detecting radiological changes in rheumatoid arthritis that are considered important by clinical experts: influence of reading with or without known sequence. J Rheumatol 2002;29(11):2306-2312.
23. Boini S, Guillemin F. Radiographic scoring methods as outcome measures in rheumatoid arthritis: properties and advantages. Ann Rheum Dis 2001 Sep;60(9):817-27

Table S1. Serious adverse events during the second year of the IMPROVED-study

	Early remission n=387	**Arm 1 n=83**	**Arm 2 n=78**	**Outside protocol n=50**
Patients with SAE, no (%)	18/387 (5%)	4/83 (5%)	7/78 (9%)	3/50 (6%)
Total number of SAE	25	5	8	3
Died	Cardiac arrest after pericarditis Kidney failure during sepsis as complications of multiple myeloma	-	Pneumococcal sepsis	-
Malignancies	Multiple myeloma Sigmoid colon carcinoma Metastases of an unknown primary tumour	Non-melanoma skin cancer, twice in 1 patient	B-cell non-Hodgkin lymphoma	-
Hospital admissions	Resection sigmoid colon carcinoma, acute coronary syndrome, aortic root replacement, 2 myocardial infarctions, diarrhoea with dehydration, respiratory distress suspected to be due to pulmonary embolism and infection, haemolytic anaemia, pulmonary embolism, 2 total knee replacements, pyelonephritis, epileptic seizure, PCI for cardiac ischemia, surgery for spinal disc herniation, 3 admissions for constipation (in 1 patient), multiple sclerosis, motorbike accident.	PCI for cardiac ischemia, interstitial lung disease, total shoulder replacement.	Pulmonary embolism, total knee replacement, pneumonia, fever with high blood pressure and abdominal lymphadenopathy (unknown cause), stroke, surgery for a fractured ankle.	Polymyalgia rheumatica, septic arthritis of the left knee, bilateral extirpation of the adnexes (cyst).

SAE: serious adverse event, PCI: percutaneous coronary intervention.

CHAPTER 6

DETERMINANTS OF DRUG FREE REMISSION IN PATIENTS WITH EARLY RHEUMATOID OR UNDIFFERENTIATED ARTHRITIS AFTER ONE YEAR OF REMISSION STEERED TREATMENT

Submitted

K.V.C. Wevers-de Boer, L. Heimans, K. Visser, A.A. Schouffoer,
E.T.H. Molenaar, J.H.L.M. van Groenendael, A.J. Peters, I. Speyer,
G. Collée, T.W.J. Huizinga, C.F. Allaart

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 and 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).

Conclusion: 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 drug free remission. Neither presence of ACPA nor other baseline characteristics were independently associated with achieving drug free remission after 1 year but in ACPA positive patients drug free remission 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 antibody (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 25mg/wk plus prednisone 60mg/day tapered in 7 weeks to 7.5mg/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 student's *t* test, Mann Whitney U test and χ^2 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 multivariable model to indentify 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, 119/375 patients (32%) 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 RA classification criteria[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 analysis 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 univariate 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), RF positivity was predictive for less often achieving DFR_{1year}, independently of TJC.

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).

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

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			
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			
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

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.
DFR_{1year}: drug free remission defined as DAS<1.6 and all medication tapered after 1 year, RF: rheumatoid factor, ACPA: anti-citrullinated protein antibody, HAQ: Health Assessment Questionnaire, DAS: disease activity score, VAS: visual analogue scale, ESR: erythrocyte sedimentation rate, RA(2010): Rheumatoid Arthritis according to the 2010 ACR/EULAR classification criteria, RA(1987): RA according to the 1987 ACR classification criteria, SHS: Sharp-van der Heijde score, Erosive: number of patients having one or more erosions, DAS-remission: defined as a DAS<1.6, ACR/EULAR remission according to the Boolean based ACR/EULAR provisional remission definition, based on 44 joint counts.

Table 2. Univariate logistic regression analyses with DFR after 1 year (yes or 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

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

remission after 1 year (DFR_{1year}), regardless of fulfilling the 1987 and/or 2010 classification criteria for RA. 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 suspect for 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 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

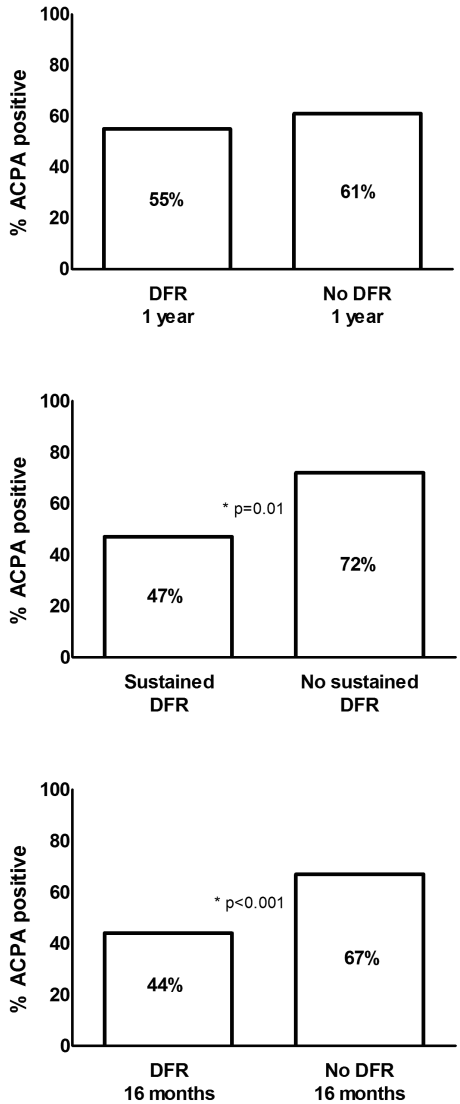

Figure 1. Percentages ACPA positive patients achieving drug free remission after 1 year versus not, sustaining drug free remission versus not and achieving drug free remission after 16 months versus not. DFR 1 year: drug free remission after 1 year, sustained DFR: patients in DFR after 1 year and after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

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 sustaining drug free remission 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 drug free remission 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.

REFERENCE LIST

1. van Tuyl LH, Vlad SC, Felson DT, Wells G, Boers M. Defining remission in rheumatoid arthritis: results of an initial American College of Rheumatology/European League Against Rheumatism consensus conference. Arthritis Rheum 2009;61(5):704-710.
2. Combe B, Landewe R, Lukas C et al. EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2007;66(1):34-45.
3. Emery P, Salmon M. Early rheumatoid arthritis: time to aim for remission? Ann Rheum Dis 1995;54(12):944-947.
4. Tiippana-Kinnunen T, Paimela L, Kautiainen H, Laasonen L, Leirisalo-Repo M. Can disease-modifying anti-rheumatic drugs be discontinued in long-standing rheumatoid arthritis? A 15-year follow-up. Scand J Rheumatol 2010;39(1):12-18.
5. Hetland ML, Stengaard-Pedersen K, Junker P et al. Radiographic progression and remission rates in early rheumatoid arthritis - MRI bone oedema and anti-CCP predicted radiographic progression in the 5-year extension of the double-blind randomised CIMESTRA trial. Ann Rheum Dis 2010;69(10):1789-1795.
6. Klarenbeek NB, van der Kooij SM, Guler-Yuksel M et al. Discontinuing treatment in patients with rheumatoid arthritis in sustained clinical remission: exploratory analyses from the BeSt study. Ann Rheum Dis 2011;70(2):315-319.
7. van der Woude D, Young A, Jayakumar K et al. Prevalence of and predictive factors for sustained disease-modifying antirheumatic drug-free remission in rheumatoid arthritis: results from two large early arthritis cohorts. Arthritis Rheum 2009;60(8):2262-2271.
8. Wevers-de Boer K, Visser K, Heimans L et al. Remission induction therapy with methotrexate and prednisone in patients with early rheumatoid and undifferentiated arthritis (the IMPROVED study). Ann Rheum Dis 2012;71(9):1472-1477.
9. Prevoo ML, van Gestel AM, van 't Hof M, van Rijswijk MH, van de Putte LB, van Riel PL. Remission in a prospective study of patients with rheumatoid arthritis. American Rheumatism Association preliminary remission criteria in relation to the disease activity score. Br J Rheumatol 1996;35(11):1101-1105.
10. Aletaha D, Neogi T, Silman AJ et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010;69(9):1580-1588.
11. Heimans L, Wevers-de Boer KV, Visser K et al. A two-step treatment strategy trial in patients with early arthritis aimed at achieving remission: the IMPROVED study. Ann Rheum Dis 2013.

12. Arnett FC, Edworthy SM, Bloch DA et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31(3):315-324.
13. van der Helm-van Mil AH, Verpoort KN, Breedveld FC, Toes RE, Huizinga TW. Antibodies to citrullinated proteins and differences in clinical progression of rheumatoid arthritis. Arthritis Res Ther 2005;7(5):R949-R958.
14. van Gaalen FA, Linn-Rasker SP, van Venrooij WJ et al. Autoantibodies to cyclic citrullinated peptides predict progression to rheumatoid arthritis in patients with undifferentiated arthritis: a prospective cohort study. Arthritis Rheum 2004;50(3):709-715.

CHAPTER 7

ASSOCIATION OF HIGH BODY MASS INDEX WITH DECREASED TREATMENT RESPONSE TO COMBINATION THERAPY IN RECENT–ONSET RHEUMATOID ARTHRITIS PATIENTS

Arthritis Care Res 2013 65(8):1235-42

L. Heimans*, M. van den Broek*, S. le Cessie, B. Siegerink, N. Riyazi, H. Han, P.J.S.M. Kerstens, T.W.J. Huizinga, W.F. Lems, C.F. Allaart

* Both authors contributed equally

ABSTRACT

Objective: To assess the association between high body mass index (BMI) and treatment response in recent-onset rheumatoid arthritis.

Methods: In the Behandelstrategieën voor Reumatoide Artritis (Treatment Strategies for Rheumatoid Arthritis) study, 508 patients were randomized to initial monotherapy or combination therapy with prednisone or infliximab (IFX). The response to Disease Activity Score (DAS) ≤2.4–steered treatment (first dose and after 1 year) was compared between patients with a BMI <25 kg/m^2 and ≥25 kg/m^2, using relative risk (RR) regression analyses. DAS, components of DAS, and functional ability during the first year were compared using linear mixed models.

Results: High BMI was independently associated with failure to achieve a DAS ≤2.4 on initial therapy (RR 1.20 [95% confidence interval (95% CI) 1.05, 1.37]). The effect for combination therapy with prednisone was RR 1.55 (95% CI 1.06, 2.28) and for combination therapy with IFX 1.42 (95% CI 0.98, 2.06). The RRs for failure after 1 year were 1.46 (95% CI 0.75, 2.83) and 2.20 (95% CI 0.99, 4.92), respectively. High BMI was also associated with failure on delayed combination therapy with IFX, after adjustment for selection bias related to previous failure on disease-modifying antirheumatic drugs. No significant association was observed in the initial monotherapy groups. In the first year, patients with a high BMI had higher DAS and worse functional ability, with more tender joints and a higher visual analogue scale global health, but not more swollen joints and similar systemic inflammation.

Conclusion: High BMI was independently associated with failure to achieve low DAS on initial combination therapy with prednisone and on initial and delayed treatment with IFX. Patients with a high BMI experienced more pain, but not more swelling or systemic inflammation.

INTRODUCTION

An association between treatment response to tumour necrosis factor (TNF) blockers and body mass index (BMI; kg/m^2) was described in a group of patients with established rheumatoid arthritis (RA) who had failed treatment on disease-modifying antirheumatic drugs (DMARDs). Patients with a high BMI responded less well to treatment with a fixed dose of the TNF blocker infliximab (IFX).[1] This finding was replicated in patients who had failed on methotrexate (MTX) and were treated with a fixed dose of adalimumab, etanercept, or IFX.[2] Patients with a high BMI and thus a higher fat mass might show more inflammation.[3, 4] Yet, clinical synovitis might be less easy to assess in RA patients with a high BMI. It has also been described that patients with various conditions and a high BMI report more pain than patients with a normal or low BMI.[5-7]

In the Behandelstrategieën voor Reumatoide Artritis (Treatment Strategies for Rheumatoid Arthritis) (BeSt) trial, a treatment to target trial in early RA patients, treatment response in terms of Disease Activity Score (DAS) and patient-reported outcomes was assessed every 3 months and yearly radiographs were taken. Because different treatment strategies were used, we were able to analyze the association between BMI and different components of treatment response not only to TNF blockers, but also to conventional DMARD monotherapy or combination therapy.

METHODS

Patients from the BeSt cohort, a study originally designed to compare 4 different treatment strategies in early DMARD-naive RA patients, were analyzed. Patients were randomized to 1 of 4 treatment groups: 1) sequential monotherapy starting with MTX, 2) step-up combination therapy starting with MTX, 3) initial combination therapy, with the COBRA (Combinatietherapie Bij Reumatoïde Artritis) scheme: MTX, sulfasalazine (SSZ), and tapered high dose prednisone, or 4) a combination of MTX and IFX.

Treatment was DAS-steered and aimed at a DAS of ≤2.4, resulting in 3 monthly treatment adjustments as long as the DAS was >2.4. Thus, in groups 1–3, delayed IFX treatment was initiated if treatment had failed on at least 3 synthetic DMARDs, including MTX, SSZ, leflunomide (in arm 1) or hydroxychloroquine (in arm 2), and prednisone (in arms 2 and 3). In all arms, DMARD treatment was changed or added to at least twice in case of insufficient response (DAS >2.4) before MTX + IFX combination therapy was started. Patients treated with MTX + IFX started IFX in a dosage of 3 mg/kg/every 8 weeks, but if the DAS remained >2.4, the IFX dosage was escalated from 3 mg/kg/2 months to 6 mg, 7.5 mg, and finally 10 mg/kg if necessary. If the highest dose did not lead to a low DAS, MTX + IFX were abandoned and the next treatment initiated. At any stage of the protocol, if patients achieved a DAS ≤2.4 for ≥6 months, treatment was tapered to maintenance dose: MTX monotherapy in groups 1 and 2, SSZ monotherapy in group 3, and MTX + IFX 3 mg/kg/2 months in group 4. More details on the treatment protocol were published previously.[8]

Treatment response (failure was defined as not achieving a DAS ≤2.4) was compared between normal weight patients (BMI <25 kg/m^2) and overweight or obese patients (BMI ≥25 kg/m^2).[9] Both height and weight were assessed at baseline and were measured by a research nurse, using professional calibrated scales to measure weight and wall-based measure rods to measure height. Treatment response was assessed at 2 time points. First, we looked at whether or not patients achieved a DAS ≤2.4 after the first 3 months of treatment. Second, we looked at failing responses (DAS >2.4) in year 1, on treatment step 1 and 2: MTX monotherapy (15 mg/week, if necessary increased to 25 mg/week) in groups 1 and 2, on combination therapy with prednisone (MTX 7.5 mg, if necessary increased to 25 mg/week) in group 3, and on treatment steps 1, 2, or 3 (MTX + IFX increased from 3 mg, 6 mg to 7.5 mg/kg/2 months) in group 4. The different cut-off for group 4 was chosen because, based on DAS evaluations before each IFX dose, treatment could be intensified every 2 months as compared to every 3 months in the other groups. We also looked for a relation between BMI and clinical response to treatment with MTX + IFX in patients who had failed treatment on previous synthetic DMARDs in groups 1–3. After 8 years of treatment, the number of protocolized treatment steps that patients had failed on was recorded in the initial treatment groups. Radiologic damage progression was assessed using the Sharp/van der Heijde score, taking the mean of the scores of 2 independent readers, blinded for patient identity, who evaluated all the radiographs of hands and feet in non-chronological order.

Statistical analyses were performed with the software program SPSS, version 17.0 (SPSS Inc., Chicago, IL), and STATA, version 12. Baseline characteristics were compared between patients with normal and high BMI using the Student's *t*-test, the Mann-Whitney U test, or the χ^2 test. To determine whether a higher BMI was associated with impaired response to therapy according to the definitions above, a relative risk (RR) regression model was used, where the parameters were estimated using a modified Poisson regression approach with robust SEs.[10] These analyses give risk ratios, which are easier to interpret than odds ratios. The analyses were adjusted for sex, age, smoking habits, rheumatoid factor (RF), and baseline DAS. Then the regression analyses for treatment response were repeated and stratified for treatment group (groups 1 and 2, group 3, and group 4). The association between BMI and failure to achieve a DAS ≤2.4 on delayed IFX was examined in patients from groups 1–3 who received MTX + IFX after failing on several DMARDs. Differences in baseline characteristics in this group, associated with response to DMARDs, were observed between patients with low or normal and high BMI, indicating that there might be a selection bias. Therefore, propensity scores with age, RF, alcohol use (yes/no), treatment group, baseline erythrocyte sedimentation rate (ESR), number of swollen joints, visual analogue scale (VAS) global and morning stiffness as predictors, and high BMI as outcome were calculated using logistic regression. Then, to correct for the differences between patients with normal and high BMI, a risk regression model was fitted with the weighting based on the estimated propensity score, i.e., 1/propensity score for patients with high BMI and 1/(1 - propensity score) for patients with

normal BMI. Weights >5 were truncated at 5. We repeated the analyses with BMI as a (linear) continuous variable. There was no evidence of a nonlinear association (tested by comparing likelihoods of different models and by using fractional polynomials). To find out whether there was a difference in disease manifestation in the first year of treatment between the BMI categories of the various DAS components or in patient-reported outcomes, linear mixed models were fitted. The following dependent variables were used in the different models: tender joint count, swollen joint count, ESR, C-reactive protein (CRP) level, patients' assessment of global health (VAS global) and of pain (VAS pain), and Health Assessment Questionnaire (HAQ) score. In each of the models, time and BMI category were entered as categorical covariates and the baseline value of the dependent variable as continuous covariate. The interaction between time and BMI was not significant in any of the analyses, therefore it was not included in the final models. The estimates were adjusted for sex, age, RF, and smoking habits.

The number of treatment steps on which patients had failed after 8 years was compared using the Mann-Whitney U test.

RESULTS

Patients with a BMI ≥25 kg/m^2 were older than patients with a BMI <25 kg/m^2 (56 years versus 53 years; p=0.03) and were less often smokers (31% versus 41%; p=0.01) (table 1). No other significant differences in baseline characteristics were observed. A BMI ≥30 kg/m^2 was observed in 15% of all patients.

High BMI was an independent predictor of failing (not achieving a DAS ≤2.4) on the first treatment step with an RR of 1.20 (95% confidence interval 95% CI 1.05;1.37) (table 2). A minor effect was observed for failing on treatment steps in year 1 (steps 1 and 2 in groups 1–3 or steps 1, 2, and 3 in group 4) with an RR of 1.15 (95% CI 0.92;1.43). Analyses were repeated with BMI as a continuous variable, and these results confirm the findings of the dichotomized analyses. High BMI was again an independent predictor of failing on the first step (RR 1.03, 95% CI 1.01;1.06) and for failing on treatment steps in year 1 (RR 1.02, 95% CI 1.01;1.04) (table 3). Adding nonlinear terms in BMI to the model did not improve the fit (p=0.99).

After 8 years of DAS-steered treatment, the median (interquartile range) number of treatment steps patients had failed on was 1 (0–3) for patients with a BMI <25 kg/m^2 and 2 (1-4) for patients with a BMI ≥25 kg/m^2 (p<0.001). The percentage of patients who after 8 years were no longer treated according to protocol due to failing on all treatment steps was not different (26% versus 22%; p=0.4).

Treatment groups

In groups 3 and 4, a higher risk of impaired response to therapy for patients with a high BMI was found with RRs of 1.55 (95% CI 1.06;2.28) and 1.42 (95% CI 0.98;2.06) for response to the first dose. For group 3, the RR for response to the first 2 treatment steps

Table 1. Baseline characteristics for patients with normal and high BMI.

	BMI<25 (n=216)	BMI≥25 (n=292)	p-value
Female, n(%)	155 (72)	188 (64)	0.08
Age	53 ± 15	56 ± 13	0.03
BMI	23 ± 2	29 ± 3	<0.001
Symptom duration, median (IQR)	23 (13-57)	23 (14-47)	0.7
ACPA positive, n(%)	131 (65)	160 (59)	0.2
RF positive, n(%)	149 (69)	180 (62)	0.09
DAS	4.4 ± 0.8	4.4 ± 0.9	0.4
HAQ	1.4 ± 0.6	1.4 ± 0.7	0.4
CRP, median (IQR)	20 (8-55)	21 (9-50)	0.96
ESR, median (IQR)	38 (20-56)	34 (18-56)	0.4
TJC, median (IQR)	13 (9-17)	13 (9-19)	0.3
SJC, median (IQR)	13 (10-19)	14 (9-18)	0.8
VAS global health	51 ± 20	54 ± 20	0.09
VAS physician	58 ± 18	57 ± 18	0.6
VAS pain	54 ± 21	55 ± 22	0.3
Smoking, n(%)	88 (41)	89 (31)	0.02

Unless indicated otherwise, values are mean ± SD.
ACPA: anti-citrullinated protein antibody, RF: rheumatoid factor, DAS: disease activity score, HAQ: Health Assessment Questionnaire, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, TJC: tender joint count, SJC: swollen joint count, VAS: visual analogue scale.

in year 1 was 1.46 (95% CI 0.75;2.83). The effect of impaired response in patients with a high BMI was stronger in group 4 (RR 2.20, 95% CI 0.99;4.92). In groups 1 and 2, no significant association between treatment response and BMI was observed.

Delayed IFX

For patients initially treated with MTX + IFX in group 4 (n=120), demographic or disease characteristics between patients with a high and low BMI were similar at baseline (data not shown). In contrast, patients with a BMI ≥25 kg/m^2 who received MTX + IFX in groups 1–3 were less often positive for anti-citrullinated protein antibody and RF (57% versus 83% and 66% versus 90%; p=0.004 and 0.002, respectively) (table S1). They were older than patients with a BMI <25 kg/m^2 (mean age 51 years versus 46 years; p=0.02). There were 32 patients with a BMI >30 kg/m^2. Of these, only 9 patients (28%) responded well to medication after 1 year. Of the patients in groups 1–3 with a BMI <30 kg/m^2, 89 of 193 (46%) responded well.

However, in crude analyses no association was seen between BMI and response to treatment in patients from groups 1–3 who received delayed MTX + IFX (RR 1.11, 95% CI 0.71;1.73) for response to first dose, and a trend was seen for response after 1 year (RR 1.56, 95% CI 0.80;3.04). After adjusting for the misbalance in the baseline characteristics

Table 2. Risk of not achieving a DAS ≤2.4 (on the first dose and during year 1) in patients with a high BMI

	Crude RR	Adjusted RR*
Fail on initial treatment step (all)	1.20 (1.04-1.38)**	1.20 (1.05-1.37)**
Fail on first dose MTX monotherapy	1.10 (0.96-1.25)	1.10 (0.97-1.25)
Fail on initial dose MTX+SSA+prednisone	1.57 (1.02-2.41)**	1.55 (1.06-2.28)**
Fail on initial dose MTX+infliximab	1.37 (0.93-2.02)	1.42 (0.98-2.06)
Fail in year 1 (all)	1.13 (0.89-1.43)	1.15 (0.92-1.43)
Fail in year 1 (groups 1+2)	1.04 (0.82-1.31)	1.05 (0.84-1.30)
Fail in year 1 (group 3)	1.37 (0.68-2.75)	1.46 (0.75-2.83)
Fail in year 1 (group 4)	2.12 (0.93-4.83)	2.20 (0.99-4.92)

First dose: MTX monotherapy in groups 1 and 2, MTX+sulfasalazine+prednisone in group 3, MTX+infliximab in group 4
Year 1: failing on treatment step 1 and 2: methotrexate monotherapy (15 or 25 mg/week) in groups 1 and 2, on combination therapy with prednisone (methotrexate 7.5 or 25 mg/week) in group 3, and on treatment steps 1, 2 or 3 (methotrexate 25 mg/week plus infliximab increased from 3, 6 to 7.5mg/kg/2 months) in group 4.
Reference: patients with a BMI <25
*adjusted for gender, age, smoking habits, rheumatoid factor (RF) and baseline DAS
** p-value <0.05

Table 3. Relative risk of not achieving a DAS ≤2.4 (on the first dose and during year 1) per unit increase of BMI (BMI as continuous variable)

	Crude RR	Adjusted RR*
Fail on initial treatment step (all)	1.025 (1.011-1.040)*	1.023 (1.010-1.037)*
Fail on first dose MTX monotherapy	1.016 (1.002-1.030)*	1.016 (1.003-1.029)*
Fail on initial dose MTX+SSA+prednisone	1.052 (1.014-1.092)*	1.049 (1.014-1.085)*
Fail on initial dose MTX+infliximab	1.029 (0.99-1.071)	1.028 (0.99-1.064)
Fail in year 1 (all)	1.032 (1.008-1.056)*	1.029 (1.005-1.055)*
Fail in year 1 (groups 1+2)	1.022 (1.002-1.043)*	1.020 (0.998-1.043)*
Fail in year 1 (group 3)	1.063 (0.97-1.165)	0.99 (0.99-1.160)
Fail in year 1 (group 4)	1.039 (0.97-1.114)	1.041 (0.98-1.112)

The legend of table 2 also applies to this table.

using propensity weighting, the RR of failure to the first dose changed to 1.37 (95% CI 0.81;2.31), and the RR of failure after 1 year changed to 2.09 (95% CI 0.97;4.49).

Disease activity components

In year 1 and adjusted for baseline differences, patients with high BMI had higher disease activity (difference in DAS 0.30, 95% CI 0.15;0.45), a higher HAQ score (difference 0.14, 95% CI 0.05;0.23), and a higher VAS pain (difference 6.2 mm [95% CI 3.0;9.4]). For DAS components, a difference was found in tender joints (difference 1.4, 95% CI 0.6;2.2) and patient's assessment of global health (VAS difference 4.9 mm, 95% CI 1.9;7.8), but not for swollen joints (difference 0.6, 95% CI -0.02;1.2) (table 4 and figure 1). Radiologic damage

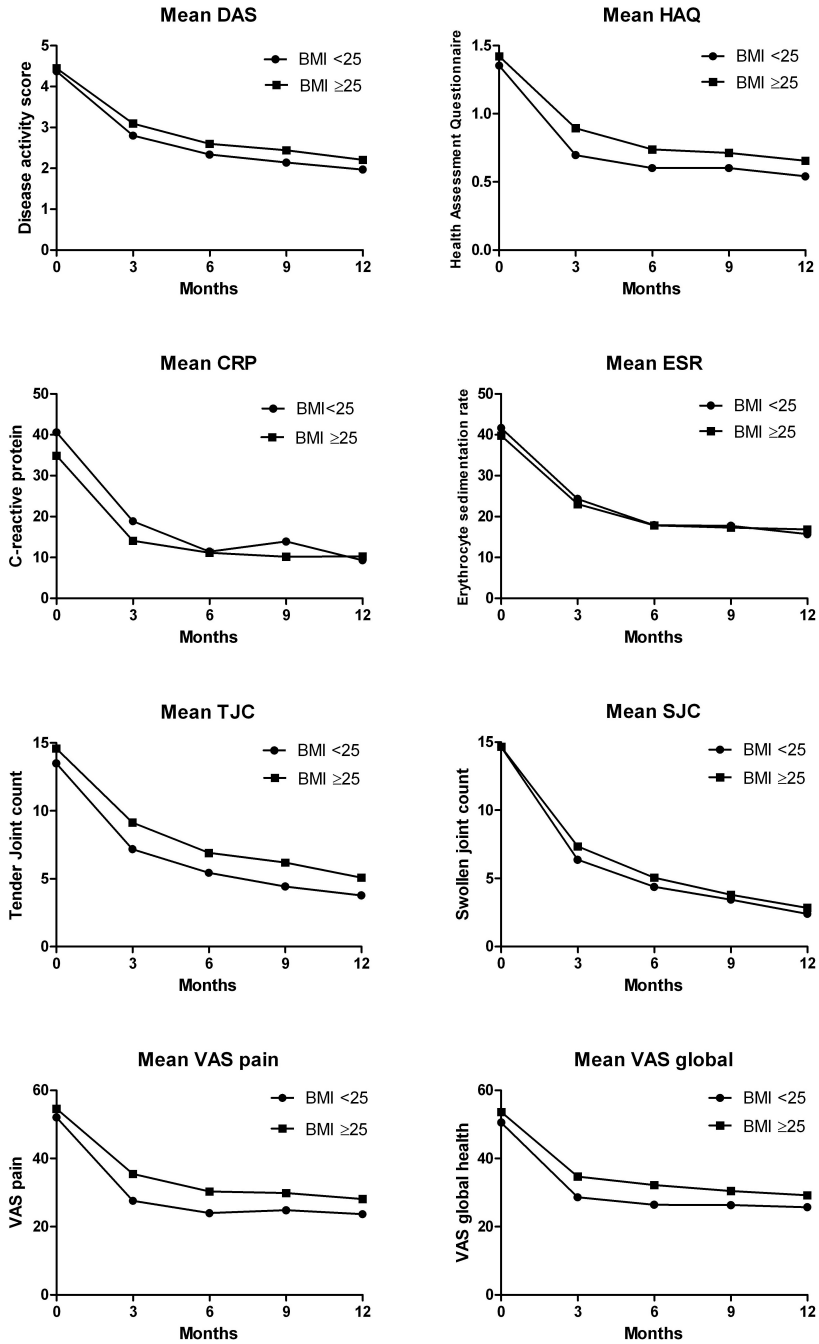

Figure 1. Disease Activity Score, Health Assessment Questionnaire, VAS global health, erythrocyte sedimentation rate, Tender joint count, Swollen joint count, patient's assessment of pain (on a visual analogue scale) and physician's assessment of disease activity in year 1 for patients with a BMI<25 and ≥25. VAS: visual analogue scale, BMI: body mass index.

Table 4. Differences in disease activity and its components for patients with a BMI≥25 compared to patients with a BMI<25 over the first year (analyzed using linear mixed models).

	Unadjusted difference	Adjusted difference*
DAS	0.25 (0.10-0.40)	0.30 (0.15-0.45)
HAQ	0.13 (0.04-0.21)	0.14 (0.05-0.23)
VAS global	4.4 (1.5-7.3)	4.9 (1.9-7.8)
ESR	0.9 (-1.3-3.1)	1.3 (-0.9-3.5)
CRP	0.1 (-2.2-2.3)	0.7 (-1.5-2.9)
TJC	1.1 (0.4-1.9)	1.4 (0.6-2.2)
SJC	0.5 (-0.1-1.1)	0.6 (-0.02-1.2)
VAS pain	5.4 (2.3-8.6)	6.2 (3.0-9.4)

*Adjusted for rheumatoid factor, age, gender and smoking habits.
DAS: Disease Activity Score, HAQ: Health Assessment Questionnaire score, VAS: visual analogue scale, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, TJC: tender joint count, SJC: swollen joint count.

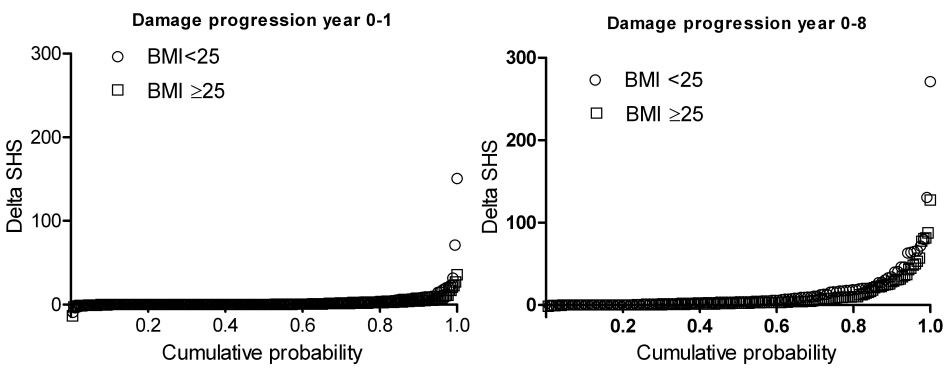

Figure 2. Cumulative probability plot of joint damage progression in year 0-1 and in years 0-8 for patients with a BMI<25 and ≥25. BMI: body mass index, SHS: Sharp/ van der Heijde Score

progression in year 1 and over 8 years follow-up was similar in patients with high or low/ normal BMI (figure 2).

DISCUSSION

In this DAS-steered treated cohort with early RA patients, high BMI was associated with failure to achieve a low DAS (≤2.4) on antirheumatic therapy, including after adjustment for confounders. This was most noticeable in patients who were treated with initial combination therapy with MTX, either combined with prednisone and SSZ, or with IFX. The association between high BMI and failure of treatment remained if the dose of MTX or IFX was increased. After stratification for initial therapy (initial monotherapy with MTX in groups 1–2, initial combination therapy with MTX, SSZ, and prednisone in group 3, or MTX and IFX in group 4), patients with a high BMI who were treated with initial

combination therapy were more likely to show a decreased response to treatment than patients with a normal BMI. This association was still seen after 1 year, after failure on the initial treatment had led to dose increases (of MTX in group 3 and of IFX in group 4), but less so in group 3 than in group 4. High BMI was also associated with failure to achieve a low DAS on delayed treatment with IFX in patients who had failed treatment on at least 3 conventional DMARDs. Due to more failure to achieve a low DAS on treatment, patients with high BMI went through significantly more treatment steps over 8 years of DAS-targeted treatment than patients with a low/normal BMI. Failure to achieve a low DAS depended mainly on the pain and joint tenderness scores, which were higher in the patients with a high BMI, whereas joint swelling and laboratory parameters of inflammation were similar in patients with high or low/normal BMI.

Recently, Klaasen et al reported that patients with a high BMI responded less well to delayed treatment with fixed-dose IFX after failure on a median of 2 DMARDs.[1] It has been suggested that this may be due to high levels of proinflammatory cytokines produced by adipocytes.[3, 4] Our results confirm that patients with a high BMI fail treatment more often on IFX, also as initial treatment, and also if the dosages are increased up to 10 mg/kg/every 8 weeks. Thus, a failure to respond on IFX in patients with higher BMI is not due to underdosing, which is also theoretically unlikely, since IFX is dosed per kilogram and the drug remains mainly in the intravascular space,[11] the volume of which can increase with higher BMI.[12] However, our data also show patients with a high BMI fail more often on treatment with a combination of MTX, SSZ, and prednisone and on subsequent treatment steps during 8 years of DAS ≤2.4–targeted treatment. Only in patients treated with initial MTX monotherapy, patients with higher BMI did not fail to achieve a low DAS more often than patients with low/normal BMI. This might be related to the fact that, in general, failure on initial MTX monotherapy was more common than on initial combination therapy, which makes it harder to analyze the role of individual risk factors.

Rather than being the result of a high ESR or swollen joint counts, the higher DAS scores in patients with higher BMI appear to depend on pain. Higher pain scores and worse global health were also reported in patients with a high BMI in a large Swedish cohort.[13] In that study, patients with a BMI ≥30 kg/m^2 also had a higher ESR and CRP level at follow-up. We found no association between a high BMI and higher parameters of inflammation or more joint swelling, but there were very few patients with a BMI ≥30 kg/m^2.

It is possible that we underestimated joint swelling in patients with a high BMI. The higher tender joint counts in patients with a high BMI might still reflect more local inflammation. We previously reported that local joint tenderness is a predictor of local joint damage after 1 year, independent of swelling.[14] This in fact supports the practice of using a composite score such as the DAS as treatment target, not merely joint swelling. We found no differences in joint damage progression after 8 years of DAS-targeted treatment in patients with high or low/normal BMI. This may be due to more treatment adjustments (because of higher DAS) in patients with high BMI, or there may be another reason why

patients with high BMI appear to be protected against joint damage progression.[15, 16] It may also be that the pain experienced by patients with high BMI does not reflect inflammation. We did not do routine assessments of fibromyalgia features, but we cannot exclude that a fibromyalgia component was present in part of these patients. Self-reported pain, especially musculoskeletal pain, is higher in patients with a high BMI, in particular with a BMI ≥30 kg/m^2, and they are more likely to report pain in multiple locations.[5, 6] The mechanism of the relationship between obesity and pain is unclear, but it is suggested that disturbances in neurotransmitters and hormones might be, at least partially, responsible.[7] This relation between BMI and pain may also influence the association between high BMI and functional disability, which was found in this cohort. Pain and body size itself may both interfere with the daily activities that are listed in the HAQ.[17]

In conclusion, in the DAS ≤2.4–targeted BeSt study we found that RA patients with a higher BMI fail more often than patients with low/normal BMI to achieve a low DAS on antirheumatic treatment. This resulted in more treatment adjustments over time. The higher DAS scores were mainly dependent on joint tenderness and self-reported pain and well-being, and were associated with less functional ability, but not with more damage progression over time.

In treatment to target strategies, finding a high DAS based on inflammation or on non-inflammatory pain may have different therapeutic consequences. Additional research, including advanced imaging techniques and biomarker studies, may further elucidate the relation between BMI and failure to treatment, thus helping us to decide how we can best treat our individual patients.

REFERENCE LIST

1. Klaasen R, Wijbrandts CA, Gerlag DM, Tak PP. Body mass index and clinical response to infliximab in rheumatoid arthritis. Arthritis Rheum 2011;63(2):359-364.
2. Gremese E, Carletto A, Padovan M et al. Obesity reduces the response rate to anti TNFalpha in rheumatoid arthritis. an approach to a personalized medicine. Arthritis Care Res (Hoboken) 2013 Jan;65(1):94-100.
3. Camhi SM, Bray GA, Bouchard C et al. The relationship of waist circumference and BMI to visceral, subcutaneous, and total body fat: sex and race differences. Obesity (Silver Spring) 2011;19(2):402-408.
4. Hotamisligil GS, Arner P, Caro JF, Atkinson RL, Spiegelman BM. Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. J Clin Invest 1995;95(5):2409-2415.
5. Hitt HC, McMillen RC, Thornton-Neaves T, Koch K, Cosby AG. Comorbidity of obesity and pain in a general population: results from the Southern Pain Prevalence Study. J Pain 2007;8(5):430-436.
6. Pradalier A, Willer JC, Boureau F, Dry J. Pain and obesity. Lancet 1980;1(8177):1090-1091.
7. Ursini F, Naty S, Grembiale RD. Fibromyalgia and obesity: the hidden link. Rheumatol Int 2011;31(11):1403-1408.
8. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. Arthritis Rheum 2005;52(11):3381-3390.
9. World Health Organization. BMI classification criteria. WHO Website 2011;http://apps.who.int/bmi/index.jsp?introPage=intro_3.html.
10. Zou G. A modified poisson regression approach to prospective studies with binary data. Am J Epidemiol 2004;159(7):702-706.

11. Klotz U, Teml A, Schwab M. Clinical pharmacokinetics and use of infliximab. Clin Pharmacokinet 2007;46(8):645-660.
12. Blouin RA, Warren GW. Pharmacokinetic considerations in obesity. J Pharm Sci 1999;88(1):1-7.
13. Ajeganova S, Andersson ML, Hafstrom I. Association of obesity with worse disease severity in rheumatoid arthritis as well as with comorbidities: a long-term followup from disease onset. Arthritis Care Res (Hoboken) 2013 Jan;65(1):78-87.
14. Klarenbeek NB, Guler-Yuksel M, van der Heijde DM et al. Clinical synovitis in a particular joint is associated with progression of erosions and joint space narrowing in that same joint, but not in patients initially treated with infliximab. Ann Rheum Dis 2010;69(12):2107-2113.
15. van der Helm-van Mil AH, van der Kooij SM, Allaart CF, Toes RE, Huizinga TW. A high body mass index has a protective effect on the amount of joint destruction in small joints in early rheumatoid arthritis. Ann Rheum Dis 2008;67(6):769-774.
16. Westhoff G, Rau R, Zink A. Radiographic joint damage in early rheumatoid arthritis is highly dependent on body mass index. Arthritis Rheum 2007;56(11):3575-3582.
17. Backholer K, Wong E, Freak-Poli R, Walls HL, Peeters A. Increasing body weight and risk of limitations in activities of daily living: a systematic review and meta-analysis. Obes Rev 2012 May;13(5):456-68.

Table S1. Baseline characteristics of patients in groups 1-3 who received delayed treatment with methotrexate+infliximab for patients with a BMI<25 and patients with a BMI ≥25.

BMI*, delayed MTX+infliximab in groups 1-3	BMI<25 n=40	BMI≥25 n=67	p-value
Female, n (%)	30 (75)	50 (75)	0.97
Age, mean ± SD	46 ± 13	51 ± 12	0.02
BMI, mean ± SD	22.1 ± 2.2	29.3 ± 3.3	<0.001
Group 1	21 (53)	34 (51)	0.97
Group 2	7 (18)	13 (19)	
Group 3	12 (30)	20 (30)	
Symptom duration, wks	27 (15-67)	28 (17-56)	0.8
ACPA positive, n (%)	33 (83)	36 (57)	0.004
RF positive, n (%)	36 (90)	44 (66)	0.005
DAS, mean ± SD	4.6 ± 0.8	4.6 ± 0.9	0.96
HAQ, mean ± SD	1.4 ± 0.6	1.4 ± 0.7	0.8
SHS, median (IQR)	2.5 (0.5-10.5)	2.5 (1.0-8.0)	0.8
ESR, median (IQR)	37 (24-62)	33 (21-55)	0.5
CRP, median (IQR)	23 (9-84)	20 (8-59)	0.2
TJC, median (IQR)	14 (9-20)	15 (11-21)	0.3
SJC, median (IQR)	15 (11-20)	13 (10-18)	0.3
VAS global, mean ± SD	50 ± 23	54 ±19	0.8
VAS physician, mean ± SD	58 ± 17	56 ±18	0.5
VAS pain, mean ± SD	56 ± 24	59 ±21	0.5
VAS morning stiffness, mean ± SD	64 ± 22	61 ±21	0.3
Smokers, n (%)	17 (43)	25 (37)	0.6
Alcohol users, n (%)	14 (35)	30 (45)	0.3

ACPA: anti-citrullinated protein antibody, RF: rheumatoid factor, DAS: disease activity score, ESR: erythrocyte sedimentation rate, TJC: tender joint count, SJC: swollen joint count, VAS global: visual analogue scale of patient's assessment of global health.

CHAPTER 8

CAN WE PREVENT RAPID RADIOLOGICAL PROGRESSION IN PATIENTS WITH EARLY ARTHRITIS?

Submitted

L. Heimans, K.V.C. Wevers-de Boer, H.K. Ronday, G. Collée,
P.B.J. de Sonnaville, B.A.M. Grillet, T.W.J. Huizinga, C.F. Allaart

ABSTRACT

Aim: Test the performance of a matrix model to predict Rapid Radiological Progression (RRP) in a study population of early rheumatoid arthritis (RA) or undifferentiated arthritis (UA) patients.

Methods: A matrix model using baseline CRP, erosion score, autoantibody status and initial treatment choice to predict RRP (increase ≥5 points in Sharp-van der Heijde Score (SHS) in 1 year) was derived from the BeSt study where patients with active RA (1987-criteria) were treated with initial monotherapy or combination therapy, aiming at low disease activity. In the IMPROVED-study, patients with early RA (2010-criteria) and UA were initially treated with methotrexate and prednisone aiming at remission. A receiver operating characteristics (ROC) curve was used to assess the discriminative value of the model to predict damage progression in the IMPROVED population.

Results: 431/479 patients with RA and 106/122 with UA could be categorized as high, intermediate, low or very low risk for RRP. One patient, with a 'very low' risk profile, showed RRP. Thirty-two other patients (5%) showed radiological progression ≥0.5 point SHS, none had a 'high risk' profile and 22 a 'very low risk' profile. The AUC of the ROC curve was 0.56 (95%CI 0.45;0.68).

Conclusion: A matrix model predicting RRP based on risk factors identified in recent onset active RA according to the 1987-criteria performed poorly in recent onset RA (2010-criteria) and UA. It appears that known risk factors for damage progression lose their impact with early remission steered treatment, so that RRP might be considered a phenomenon of the past.

INTRODUCTION

Early treatment in patients with rheumatoid arthritis (RA) can prevent joint damage progression and thus preserve functional ability.[1] Risk factors for rapid progression of radiological joint damage can be used to try to predict which patients require more progressive initial treatment to prevent damage and in whom the focus can be more on symptom reduction alone. To facilitate this, we previously developed a matrix model predicting Rapid Radiological Progression (RRP) defined as an increase in Sharp-van der Heijde Score (SHS) of ≥5 points in 1 year.[2, 3] The model was based on risk factors for RRP identified in patients with recent onset active RA (ACR 1987 classification criteria) who participated in the BeSt study: baseline ESR or CRP, baseline erosion score, autoantibody profile and initial treatment.[4] Following up on the BeSt study, in the IMPROVED study we included patients with RA (2010 classification criteria) or undifferentiated arthritis (UA) clinically suspect for RA, with a more recent symptom onset than the BeSt population. Disease activity at baseline was less severe and all started with initial combination therapy with methotrexate and a tapered high dose of prednisone, if necessary followed up with treatment adjustments until remission was achieved. We investigated how the BeSt matrix model performed in the IMPROVED population.

METHODS

The IMPROVED-study is a multi-center clinical trial in which RA and UA patients were initially treated with methotrexate (MTX) 25mg/wk and prednisone 60mg/day tapered to 7.5mg/day in 7 weeks. If patients achieved early remission (Disease Activity Score DAS<1.6 after 4 months), medication was tapered. Patients not in early remission after 4 months were randomized either to MTX 25 mg/wk plus hydroxychloroquine (HCQ) 400mg/day, sulphasalazine (SSZ) 2000mg/day and prednisone 7.5mg/day (arm 1) or to MTX 25mg/wk plus adalimumab (ADA) 40mg/2weeks (arm 2). During follow-up medication was increased or switched in case of no remission and tapered or stopped in case of remission.[5]

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 (LH and KW). Both readers gave similar progression scores (difference <2 points) in 83% of all patients. In 54 patients with inter-reader differences ≥2 in progression score, a consensus score was reached.

The matrix model to predict RRP was derived from the BeSt-study. The model visualizes the risk for RRP which was predicted based on CRP and number of erosions at baseline, status for rheumatoid factor (RF) and/or anti-citrullinated protein antibody (ACPA) and initial treatment choice (initial monotherapy or initial combination therapy with prednisone or infliximab).[6] The predicted risk for RRP is indicated by coloured boxes which indicates the 'risk profile' of a patient; red represents a high risk (≥50% risk of RRP), orange means an intermediate risk (20-50%), yellow boxes indicate a low risk (10-20%) and green boxes a very low risk (<10%).

To investigate if patients in the IMPROVED-study could be identified as having high, intermediate or low risk for RRP, we used the matrix model variant for patients treated with initial combination therapy with prednisone and assigned each IMPROVED patient according to presence or absence of the various aforementioned risk factors. Then we added the number of IMPROVED patients per matrix box, with the number in the coloured box indicating the actual number of patients with that combination of risk factors.

In a separate test, the matrix model was then used to explore if it could help to identify patients who showed with any radiological progression (≥0.5 point increase SHS) after year 1. Positive and negative predicted values were calculated and the area under the curve (AUC) of the receiver operating characteristics (ROC) curve to explore the discriminative value of the matrix in predicting radiological progression ≥0.5.

For all analyses SPSS version 20.0 (SPSS Inc., Chicago, IL) was used.

RESULTS

In the IMPROVED-study 610 patients were included, 479 patients with early RA (according to the 2010 ACR classification criteria [7]) and 122 patients with undifferentiated arthritis (UA). Nine patients could not be classified because of insufficient data. For 431 RA patients and 106 UA patients sufficient baseline characteristics were available to categorize them in the matrix model (figure 1).

Based on the matrix model, no patients were estimated to have high risk for RRP. Thirteen patients with RA and no patients with UA were identified as having an intermediate risk of RRP. None of those showed RRP, 2 showed progression ≥0.5 SHS. Fifty-eight patients with RA and no patients with UA were predicted to have a low risk of RRP, and none of those showed RRP, but 5 showed progression ≥0.5 SHS. The remaining 360 patients with RA and all 106 patients with UA were identified as having very low risk for RRP. One of those patients with RA actually did show RRP and in total 30 RA and 2 UA patients showed progression≥0.5 SHS (1 patient who could not be classified also showed progression). The median (IQR) progression in SHS was 0 (0-0) in both patients with RA and patients with UA.

In RA patients the PPV of the matrix model for progression≥0.5 SHS, based on an intermediate or higher risk for progression, was 15.4%. The NPV of the matrix model for no progression was 98.8%. In UA patients the PPV and NPV could not be calculated since all 106 patients had the same risk. The AUC of the ROC curve for progression≥0.5 SHS was 0.56 (95%CI 0.45;0.68, p=0.27).

DISCUSSION

A matrix model to predict rapid radiological progression which we previously developed based on results of RA patients in the BeSt study, was not useful to predict damage progression in patients with UA and early RA who participated in the IMPROVED-study. This is likely due to differences in inclusion criteria in both studies, in combination with treatment effects.

A

RA	RF/ACPA -/-	-/+ or +/-	+/+	
CRP ≥ 35	0 #	0 *	0 *	Erosions ≥4
	2	4 #	13 *	Erosions 1-3
	11	19 #	35 #	Erosions 0
CRP 10-34.99	0	0 #	0 #	Erosions ≥4
	2	4	15	Erosions 1-3
	23	28	81 (1 patient with RRP)	Erosions 0
CRP < 10	0	0	0 #	Erosions ≥4
	4	5	19	Erosions 1-3
	35	45	86	Erosions 0

B.

UA	RF/ACPA -/-	-/+ or +/-	+/+	
CRP ≥ 35	0 #	0 *	0 *	Erosions ≥4
	5	0 #	0 *	Erosions 1-3
	12	0 #	0 #	Erosions 0
CRP 10-34.99	0	0 #	0 #	Erosions ≥4
	3	0	0	Erosions 1-3
	32	0	0	Erosions 0
CRP < 10	0	0	0 #	Erosions ≥4
	3	0	1	Erosions 1-3
	46	2	2	Erosions 0

Figure 1. The number of patients with a combination of baseline risk factors in patients with RA and patients with UA. The numbers in the boxes represent the actual number of patients with that combination of risk factors for patients with A) Rheumatoid Arthritis (RA) and B) Undifferentiated arthritis (UA). Orange boxes (*) represent an intermediate risk of Rapid Radiological Progression (RRP) (20-50%), yellow boxes (#) a low risk (10-20%) and green boxes a very low risk (10%). In total, 47 of 479 RA-patients and 16 of 122 UA-patients could not be classified because of insufficient data.

Baseline disease activity and symptom duration appeared to be lower in the IMPROVED-study than in the BeSt study. In the BeSt population, only RA patients who fulfilled the 1987 classification criteria and who had high disease activity were included. Following recommendations to identify and treat RA patients as early as possible, in the IMPROVED-study, RA patients were included and treated when they fulfilled the 2010 classification criteria. Also, patients with UA clinically suspected by the treating rheumatologist to have early RA were included. In addition, all IMPROVED patients received initial combination therapy with methotrexate and prednisone, whereas half of the BeSt patients had received initial MTX monotherapy. As a consequence, not only were baseline disease activity lower and symptom duration shorter in the IMPROVED-study, also the risk factors used in the matrix model, were less often present in the

IMPROVED patients than in the BeSt patients: they had lower CRP values, were less often erosive at baseline and less often ACPA and/or RF positive, and none received initial MTX monotherapy. Thus rapid radiologic damage progression was less likely in most IMPROVED patients, and particularly unlikely in the UA patients.

Based on the matrix model, thirteen patients had an intermediate risk of RRP. Of those, 2 showed progression ≥0.5 SHS in year 1, the others showed no progression. This is possibly related to targeted treatment aiming at remission (DAS<1.6) in the IMPROVED-study, which resulted in suppression of disease activity. One patient predicted to have low risk actually showed RRP, suggesting that other risk factors for damage progression may be present that are not included in the matrix model.

It appears that by treating arthritis patients earlier and with remission targeted therapy, RRP and indeed also minimal radiologic damage progression may be prevented. Prediction models based on data from previous trials and patients populations and times of less strict treatment strategies to predict joint damage may thus no longer be relevant for current and future patients. As it is still possible that residual disease activity will affect cartilage and bone in and around arthritic joints, newer techniques to monitor these effects may need to be employed or developed, and next, new risk factors for joint damage may be identified.

REFERENCE LIST

1. Welsing PM, van Gestel AM, Swinkels HL, Kiemeney LA, van Riel PL. The relationship between disease activity, joint destruction, and functional capacity over the course of rheumatoid arthritis. Arthritis Rheum 2001;44(9):2009-2017.
2. Bruynesteyn K, van der Heijde D, Boers M et al. Determination of the minimal clinically important difference in rheumatoid arthritis joint damage of the Sharp/van der Heijde and Larsen/Scott scoring methods by clinical experts and comparison with the smallest detectable difference. Arthritis Rheum 2002;46(4):913-920.
3. Bruynesteyn K, van der Heijde D, Boers M et al. Detecting radiological changes in rheumatoid arthritis that are considered important by clinical experts: influence of reading with or without known sequence. J Rheumatol 2002;29(11):2306-2312.
4. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. Arthritis Rheum 2005;52(11):3381-3390.
5. Heimans L, Wevers-de Boer KV, Visser K et al. A two-step treatment strategy trial in patients with early arthritis aimed at achieving remission: the IMPROVED study. Ann Rheum Dis 2013.
6. Visser K, Goekoop-Ruiterman YP, de Vries-Bouwstra JK et al. A matrix risk model for the prediction of rapid radiographic progression in patients with rheumatoid arthritis receiving different dynamic treatment strategies: post hoc analyses from the BeSt study. Ann Rheum Dis 2010;69(7):1333-1337.
7. Aletaha D, Neogi T, Silman AJ et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010;69(9):1580-1588.

CHAPTER 9

FOUR-MONTH METACARPAL BONE MINERAL DENSITY LOSS PREDICTS RADIOLOGICAL JOINT DAMAGE PROGRESSION AFTER 1 YEAR IN PATIENTS WITH EARLY RHEUMATOID ARTHRITIS – EXPLORATORY ANALYSES FROM THE IMPROVED-STUDY

Accepted for publication in Annals of the Rheumatic Diseases

K.V.C. Wevers-de Boer, L. Heimans, K. Visser, J. Kälvesten,
J.A.P.M. Ewals, E.T.H. Molenaar, J. Groenendael, A. Peeters,
I Speyer, G. Collee, T.W.J. Huizinga, C.F. Allaart

ABSTRACT

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

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 (DAS<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 for progression (OR (95%CI) 2.0 (1.4-2.9)).

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

Peri-articular 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 four months of treatment, as measured by Digital X-ray Radiogrammetry (DXR-BMD), may be a predictor of radiological joint damage progression after one year in patients with undifferentiated or early rheumatoid arthritis 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 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 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/wk plus hydroxychloroquine (HCQ) 400mg/day, sulphasalazine (SSZ) 2000mg/day and prednisone 7.5mg/day (arm 1) or to MTX 25mg/wk plus adalimumab (ADA) 40mg/2weeks (arm 2). Some patient 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 of whom radiologic 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 antibody (ACPA) and Rheumatoid Factor (RF) status. At baseline and every 4 months, the following clinical and laboratory variables were collected: Disease Activity Score (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 which automatically recognises three regions of interest 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.[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 were 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 included in this analysis 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, those 2 univariate significant predictors (using a significance level of 0.10) with the highest effect size were selected for multiple regression. As radiologic 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 (SPSS Inc., Chicago, IL).

RESULTS

Clinical characteristics

We included 428 patients in the current analysis. 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 not. Of those with radiological progression, 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, 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 in patients with radiological progression (median (IQR) -9.6 (-15.2;-2.7) than in patients without (-2.0 (-7.2;2.5), 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). The one patient with rapid radiological progression (18 points after 1 year) had DXR-BMD loss 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

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.

	Total population	Radiologic progression		p-value
		Yes	No	
Baseline	n=428	n=28	n=400	
Age, years, mean ± SD	52 ± 13	58 ± 11	52 ± 13	0.01
Female, n (%)	294 (69)	22 (79)	272 (68)	0.2
BMI, kg/m^2, mean ± SD	26 ± 4	25 ± 4	26 ± 4	0.6
Current smoking, n (%)	127 (30)	11 (39)	116 (29)	0.3
Current alcohol use, n (%)	250 (58)	17 (61)	233 (58)	0.9
Postmenopausal status, n (%)	156 (53)	17 (89)	139 (58)	0.01
Previous fractures, n (%)	142 (33)	8 (29)	134 (34)	0.7
Familial osteoporosis, n (%)	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), n (%)	344 (80)	26 (93)	318 (80)	0.04
Symptom duration, wks, median (IQR)	18 (9-33)	20 (9-47)	18 (9-32)	0.5
ACPA positive, n (%)	247 (58)	23 (82)	224 (56)	0.008
RF positive, n (%)	241 (56)	18 (64)	223 (56)	0.2
ACPA and RF positive, n (%)	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, n (%)	62 (14)	11 (39)	51 (13)	<0.001
4 months				
DAS, mean ± SD	1.5 ± 0.9	1.5 ±0.8	1.5 ± 0.9	0.9
Remission, n (%)	275 (64)	17 (61)	258 (65)	0.7
Early remission Group, n (%)	281 (66)	17 (61)	264 (66)	0.6
Arm 1 MTX+SSZ+HCQ+pred, n (%)	60 (14)	4 (14)	56 (14)	0.97
Arm 2 MTX+adalimumab, n (%)	57 (13)	5 (18)	52 (13)	0.5
Outside of Protocol Group, n (%)	30 (7)	2 (7)	28 (7)	0.98
8 months				
DAS, mean ± SD	1.5 ± 0.8	1.8 ± 1.0	1.5 ± 0.8	0.05
Remission, n (%)	246 (57)	12 (43)	234 (61)	0.1
1 year				
Use of Bisphosphonate, n (%)	129 (30)	9 (32)	120 (30)	0.8
Use of Calcium and/or vitamine D, n (%)	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, n (%)	235 (55)	16 (57)	219 (55)	0.8
SHS progression, median (IQR)	0 (0-0)	0.5 (0.5-1.4)	0 (0-0)	<0.001

BMI: Body Mass Index (kg/m2), DAS: Disease Activity Score, RA (2010): rheumatoid arthritis according to the ACR/EULAR 2010 classification criteria, ACPA: anti-citrullinated protein antibody, RF: rheumatoid factor, SHS: Sharp- van der Heijde Score, presence of erosions: defined as ≥1 erosions, remission: defined as DAS<1.6, early remission group: patients who were in remission after 4 months and started tapering medication, 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, MTX: methotrexate, SSZ: sulfasalazine, HCQ: hydroxychloroquine, pred: prednisone, outside of protocol group: patients not in early remission but not randomized and treated outside the protocol.

Table 2. DXR-BMD measurements and changes in DXR-BMD during the first study year of the total study population and separate for patients with and without radiological progression.

	Time point (months)	Total n=428	SHS progression		p-value
			Yes: n=28	No: n=400	
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

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

zero, 9 (32%) had not achieved early remission and were randomized, and 2 were treated outside the protocol. Of those 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).

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 TJC (p=0.05). Female gender, presence of either ACPA or RF, symptom duration, baseline erosion score and 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 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 for 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 (18 points after 1 year), the results above did not significantly change (data not shown).

Table 3a. Univariate logistic regression analysis with radiological progression as binomial dependent variable.

	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
Erosions 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

RA: rheumatoid arthritis (according to the 2010 ACR/EULAR classification criteria), presence of baseline erosions: ≥1 erosions, ACPA: anti-citrullinated protein antibody, RF: rheumatoid factor, DXR-BMD: metacarpal bone mineral density measured by digital X-ray radiogrammetry, erosion score: Sharp-van der Heijde erosion score, tSHS: total Sharp-van der Heijde Score, ESR: erythrocyte sedimentation rate in mm/hr, CRP: C-reactive protein, TJC: tender joint count, early remission group: patients who were in remission after 4 months and started tapering medication, 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, early DAS-remission: remission (DAS<1.6) after 4 months.

Table 3b. Multivariate logistic regression with radiologic progression as binomial dependent variable.

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

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

Patients without baseline erosions

In 366 (86%) patients no baseline erosions were present, of which 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) in patients with progression and -2.0 (-7.0;2.4) mg/cm^2 in patients without (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 entering 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).

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 for 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 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 have been formulated.[14] In the IMPROVED trial we included 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 this 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.

Table 4a. Univariate logistic regression analysis with radiological progression as binomial 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

RA: rheumatoid arthritis (according to 2010 ACR/EULAR classification criteria), ACPA: anti-citrullinated protein antibody, RF: rheumatoid factor, DXR-BMD: metacarpal bone mineral density measured by digital X-ray radiogrammetry, SHS: Sharp-van der Heijde Score, ESR: erythrocyte sedimentation rate in mm/hr, CRP: C-reactive protein, TJC: tender joint count, early remission group: patients who were in remission after 4 months and started tapering medication, 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, early DAS-remission: remission (DAS<1.6) after 4 months.

Table 4b. Multivariate logistic regression with radiologic progression as binomial 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

DXR-BMD: metacarpal bone mineral density measured by digital X-ray radiogrammetry, SHS: Sharp-van der Heijde Score, OR: odds ratio, CI: confidence interval.

To individualize treatment, predictive factors for damage progression have been identified and prediction models build.[4, 6, 7] But in particular in patients without baseline damage, predicting who will develop joint damage may be difficult. We looked at 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 indeed 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 for 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 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 may be the fact that, due to the inclusion of patients with early and relatively mild disease, progressively treated with the aim of achieving remission, only very 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 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 than on the fact that 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 made 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 will be applied in clinical practice using the DXR online method, neither low precision or missing values may be problematic, as X-rays will then be made 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 could 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.

REFERENCE LIST

1. Finckh A, Liang MH, van Herckenrode CM, de Pablo P. Long-term impact of early treatment on radiographic progression in rheumatoid arthritis: A meta-analysis. Arthritis Rheum 2006;55(6):864-872.
2. Klarenbeek NB, Guler-Yuksel M, van der Kooij SM et al. The impact of four dynamic, goal-steered treatment strategies on the 5-year outcomes of rheumatoid arthritis patients in the BeSt study. Ann Rheum Dis 2011;70(6):1039-1046.
3. Boers M, Verhoeven AC, Markusse HM et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet 1997;350(9074):309-318.
4. Visser K, Goekoop-Ruiterman YP, de Vries-Bouwstra JK et al. A matrix risk model for the prediction of rapid radiographic progression in patients with rheumatoid arthritis receiving different dynamic treatment strategies: post hoc analyses from the BeSt study. Ann Rheum Dis 2010;69(7):1333-1337.
5. van der Helm-van Mil AH, le Cessie S, van Dongen H, Breedveld FC, Toes RE, Huizinga TW. A prediction rule for disease outcome in patients with recent-onset undifferentiated arthritis: how to guide individual treatment decisions. Arthritis Rheum 2007;56(2):433-440.
6. Vastesaeger N, Xu S, Aletaha D, St Clair EW, Smolen JS. A pilot risk model for the prediction of rapid radiographic progression in rheumatoid arthritis. Rheumatology (Oxford) 2009;48(9):1114-1121.
7. Visser H, le Cessie S, Vos K, Breedveld FC, Hazes JM. How to diagnose rheumatoid arthritis early: a prediction model for persistent (erosive) arthritis. Arthritis Rheum 2002;46(2):357-365.
8. Brook A, Corbett M. Radiographic changes in early rheumatoid disease. Ann Rheum Dis 1977;36(1):71-73.
9. Haugeberg G, Green MJ, Quinn MA et al. Hand bone loss in early undifferentiated arthritis: evaluating bone mineral density loss before the development of rheumatoid arthritis. Ann Rheum Dis 2006;65(6):736-740.
10. Dirven L, Guler-Yuksel M, de Beus WM et al. Changes in hand bone mineral density and the association with the level of disease activity in patients with rheumatoid arthritis: bone mineral density measurements in a multicenter randomized clinical trial. Arthritis Care Res (Hoboken) 2011;63(12):1691-1699.
11. Forslind K, Boonen A, Albertsson K, Hafstrom I, Svensson B. Hand bone loss measured by digital X-ray radiogrammetry is a predictor of joint damage in early rheumatoid arthritis. Scand J Rheumatol 2009;38(6):431-438.
12. Hoff M, Haugeberg G, Odegard S et al. Cortical hand bone loss after 1 year in early rheumatoid arthritis predicts radiographic hand joint damage at 5-year and 10-year follow-up. Ann Rheum Dis 2009;68(3):324-329.
13. Guler-Yuksel M, Klarenbeek NB, Goekoop-Ruiterman YP et al. Accelerated hand bone mineral density loss is associated with progressive joint damage in hands and feet in recent-onset rheumatoid arthritis. Arthritis Res Ther 2010;12(3):R96.
14. Aletaha D, Neogi T, Silman AJ et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010;69(9):1580-1588.
15. Prevoo ML, van Gestel AM, van t Hof M, van Rijswijk MH, van de Putte LB, van Riel PL. Remission in a prospective study of patients with rheumatoid arthritis. American Rheumatism Association preliminary remission criteria in relation to the disease activity score. Br J Rheumatol 1996;35(11):1101-1105.
16. Wevers-de Boer K, Visser K, Heimans L et al. Remission induction therapy with methotrexate and prednisone in patients with early rheumatoid and undifferentiated arthritis (the IMPROVED study). Ann Rheum Dis 2012.
17. Heimans L, Wevers-de Boer KV, Visser K et al. A two-step treatment strategy trial in patients with early arthritis aimed at achieving remission: the IMPROVED study. Ann Rheum Dis 2013.

18. van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. J Rheumatol 2000;27(1):261-263.
19. Rosholm A, Hyldstrup L, Backsgaard L, Grunkin M, Thodberg HH. Estimation of bone mineral density by digital X-ray radiogrammetry: theoretical background and clinical testing. Osteoporos Int 2001;12(11):961-969.
20. Donders AR, van der Heijden GJ, Stijnen T, Moons KG. Review: a gentle introduction to imputation of missing values. J Clin Epidemiol 2006;59(10):1087-1091.
21. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol 1996;49(12):1373-1379.
22. Steyerberg EW, Eijkemans MJ, Habbema JD. Stepwise selection in small data sets: a simulation study of bias in logistic regression analysis. J Clin Epidemiol 1999;52(10):935-942.
23. Davies HT, Crombie IK, Tavakoli M. When can odds ratios mislead? BMJ 1998;316(7136):989-991.
24. Bruynesteyn K, van der Heijde D, Boers M et al. Determination of the minimal clinically important difference in rheumatoid arthritis joint damage of the Sharp/van der Heijde and Larsen/Scott scoring methods by clinical experts and comparison with the smallest detectable difference. Arthritis Rheum 2002;46(4):913-920.
25. Smolen JS, Landewe R, Breedveld FC et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis 2010;69(6):964-975.
26. Dhainaut A, Hoff M, Kalvesten J, Lydersen S, Forslind K, Haugeberg G. Long-term in-vitro precision of direct digital X-ray radiogrammetry. Skeletal Radiol 2011;40(12):1575-1579.
27. Haugeberg G, Strand A, Kvien TK, Kirwan JR. Reduced loss of hand bone density with prednisolone in early rheumatoid arthritis: results from a randomized placebo-controlled trial. Arch Intern Med 2005;165(11):1293-1297.
28. Hoff M, Haugeberg G, Kvien TK. Hand bone loss as an outcome measure in established rheumatoid arthritis: 2-year observational study comparing cortical and total bone loss. Arthritis Res Ther 2007;9(4):R81.
29. Black DM, Palermo L, Sorensen T et al. A normative reference database study for Pronosco X-posure System. J Clin Densitom 2001;4(1):5-12.

CHAPTER 10

THE RELATIONSHIP BETWEEN DISEASE ACTIVITY AND DEPRESSIVE SYMPTOMS SEVERITY AND OPTIMISM – RESULTS FROM THE IMPROVED-STUDY

Clin Rheumatol 2013 32(12):1751-7

L. Heimans, K.V.C. Wevers-de Boer, K. Visser, H.K. Ronday,
G.M. Steup-Beekman, M. van Oosterhout, T.W.J. Huizinga,
E.J. Giltay, R.C. van der Mast, C.F. Allaart

ABSTRACT

Objectives: 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 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 25 mg/week and prednisone 60 mg/day (tapered to 7.5 mg/day in 7 weeks). Linear regression analysis was used to assess the association between the disease activity score (DAS) and its components (tender joint count, general well-being measured with a visual analogue scale (VAS), swollen joint count, and erythrocyte sedimentation rate) 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.

Conclusion: 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

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 ACR/EULAR 2010 classification criteria[12] with a duration of symptoms ≤2 years. UA patients had at least one joint clinically assessed as 'arthritis' and at least one 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 that were recruited between March 2007 and September 2010 were at least 18 years old, disease modifying anti-rheumatic drug naïve, and had a disease activity score (DAS) ≥1.6. Exclusion criteria included pregnancy, malignancy within the last 5 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 for the first 4 months with methotrexate 25 mg/week and prednisone 60 mg/day, tapered to 7.5 mg/day in 7 weeks.

At baseline and after 4 months, a trained assessor performed a full joint evaluation and calculated a DAS. The patients were asked to fill out a visual analogue scale (VAS) for global well-being, the Health Assessment Questionnaire (HAQ),[13] 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).[14, 15]

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.[14]

Dispositional optimism was assessed by using the LOT-R. The LOT-R is a 10-item continuous scale to measure optimism.[15] The questionnaire consists of six score items and four 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 and higher scores indicate greater optimism. Low dispositional optimism has previously been defined as a total score <12 (often yielding ±20 % of the subjects with the lowest scores).[16] Missing values were replaced with the rounded mean of the remaining score items if at least four of the six score items were filled out.[17] Previously, college students in the USA scored a mean (standard deviation (SD)) LOT-R score of 14.3 (4.3); patients after bypass surgery scored 15.2 (4.1).[15]

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 χ^2 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 well-being, 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[18]) 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 20.0 (SPSS Inc., Chicago, IL).

RESULTS

Characteristics of participants

Six hundred ten patients were included in the IMPROVED-study of whom 222 patients gave informed consent to also 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 completed 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 LOT-R 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, three reported using antidepressants and two 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 well-being, 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 BDI-II score in the entire group from 8.5 (SD 7.7) at baseline to 7.0 (SD 7.2) (95% CI -2.3; -0.6, p=0.001). Depressive symptoms after treatment were minimal, only 21 out of 215 (9.8 %) had mild depressive symptoms (BDI-II score 14–19), 11 out of 215 (5.1 %) had moderate (BDI-II score 20–28), and 5 out of 215 patients (2.3 %) had severe depressive symptoms (BDI-II >29). After 4 months, 138 patients (66 %) had achieved clinical remission, with a mean (SD) DAS of 0.9 (0.4). BDI-II scores after 4 months

Table 1. Baseline characteristics of 222 patients who filled out BDI-II and optimism questionnaires compared to all patients included in the IMPROVED study.

	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 are presented as means ± standard deviations (SD), medians and interquartile ranges (IQR), or numbers and percentages (%) when appropriate. DAS: disease activity score, ACPA: anti-citrullinated protein antibody, ESR: erythrocyte sedimentation rate, VAS: visual analogue scale, HAQ: health assessment questionnaire, BDI-II: Beck Depression Inventory II, LOT-R: Life Orientation Test Revised.
*Data of patients who filled out at least one of the questionnaires, at one of the time points.

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 the patients who did not (p<0.001, figure 1).

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).

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[1,2] (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		
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		
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.

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.

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,

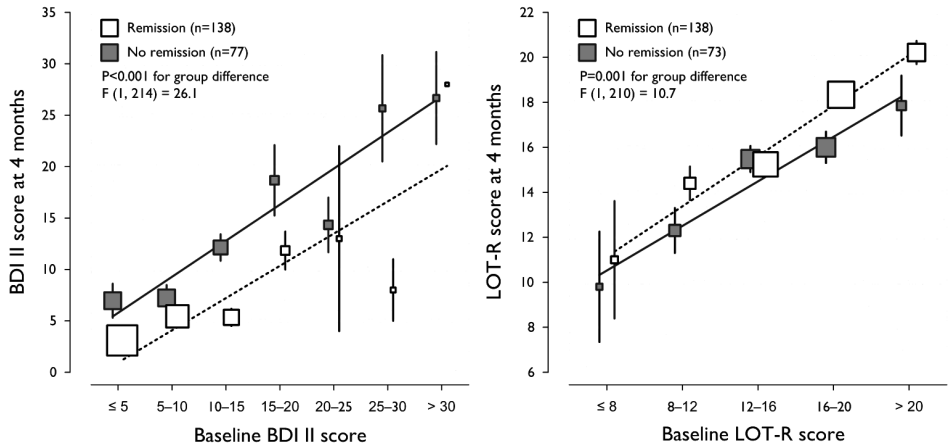

Figure 1. Difference between the patients with and without remission. The size of each square is proportional to the number of patients. Univariate regression lines are shown. P-values by analysis of covariance for the group difference, while adjusting for baseline values. Continuous values were used 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.

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, it is 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 extent of joint tenderness on examination and reported global well-being 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,[19] while patients who have more severe depressive symptoms may also be more susceptible for and report more pain.[20-22] 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.[23] 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.[17, 24, 25]

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 that 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.[26-28]

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 achieve remission than in patients who do 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.

REFERENCE LIST

1. Dickens C, McGowan L, Clark-Carter D, Creed F. Depression in rheumatoid arthritis: a systematic review of the literature with meta-analysis. Psychosom Med 2002;64(1):52-60.
2. Covic T, Tyson G, Spencer D, Howe G. Depression in rheumatoid arthritis patients: demographic, clinical, and psychological predictors. J Psychosom Res 2006;60(5):469-476.
3. Kekow J, Moots R, Khandker R, Melin J, Freundlich B, Singh A. Improvements in patient-reported outcomes, symptoms of depression and anxiety, and their association with clinical remission among patients with moderate-to-severe active early rheumatoid arthritis. Rheumatology (Oxford) 2011;50(2):401-409.
4. Pincus T, Griffith J, Pearce S, Isenberg D. Prevalence of self-reported depression in patients with rheumatoid arthritis. Br J Rheumatol 1996;35(9):879-883.
5. O'Brien SM, Scott LV, Dinan TG. Cytokines: abnormalities in major depression and implications for pharmacological treatment. Hum Psychopharmacol 2004;19(6):397-403.
6. Maes M, Bosmans E, De JR, Kenis G, Vandoolaeghe E, Neels H. Increased serum IL-6 and IL-1 receptor antagonist concentrations in major depression and treatment resistant depression. Cytokine 1997;9(11):853-858.
7. Da Silva JA, Jacobs JW, Kirwan JR et al. Safety of low dose glucocorticoid treatment in rheumatoid arthritis: published evidence and prospective trial data. Ann Rheum Dis 2006;65(3):285-293.
8. Fietta P, Fietta P, Delsante G. Central nervous system effects of natural and synthetic glucocorticoids. Psychiatry Clin Neurosci 2009;63(5):613-622.
9. Huscher D, Thiele K, Gromnica-Ihle E et al. Dose-related patterns of glucocorticoid-induced side effects. Ann Rheum Dis 2009;68(7):1119-1124.
10. Brown ES. Effects of glucocorticoids on mood, memory, and the hippocampus. Treatment and preventive therapy. Ann N Y Acad Sci 2009;1179:41-55.
11. Scheier MF, Carver CS. Optimism, coping, and health: assessment and implications of generalized outcome expectancies. Health Psychol 1985;4(3):219-247.
12. Aletaha D, Neogi T, Silman AJ et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010;69(9):1580-1588.
13. Siegert CE, Vleming LJ, Vandenbroucke JP, Cats A. Measurement of disability in Dutch rheumatoid arthritis patients. Clin Rheumatol 1984;3(3):305-309.
14. Beck A. BDI-II-NL: De Nederlandse versie van de Beck depression inventory 2nd ed. 2002.
15. Scheier MF, Carver CS, Bridges MW. Distinguishing optimism from neuroticism (and trait anxiety, self-mastery, and self-esteem): a reevaluation of the Life Orientation Test. J Pers Soc Psychol 1994;67(6):1063-1078.
16. van de Rest O, de Goede J, Sytsma F et al. Association of n-3 long-chain PUFA and fish intake with depressive symptoms and low dispositional optimism in older subjects with a history of myocardial infarction. Br J Nutr 2010;103(9):1381-1387.

17. Zenger M, Glaesmer H, Hockel M, Hinz A. Pessimism predicts anxiety, depression and quality of life in female cancer patients. Jpn J Clin Oncol 2011;41(1):87-94.
18. Prevoo ML, van Gestel AM, van 't Hof M, van Rijswijk MH, van de Putte LB, van Riel PL. Remission in a prospective study of patients with rheumatoid arthritis. American Rheumatism Association preliminary remission criteria in relation to the disease activity score. Br J Rheumatol 1996;35(11):1101-1105.
19. Margaretten M, Julian L, Katz P, Yelin E. Depression in patients with rheumatoid arthritis: description, causes and mechanisms. Int J Clin Rheumtol 2011;6(6):617-623.
20. Ryerson CJ, Arean PA, Berkeley J et al. Depression is a common and chronic comorbidity in patients with interstitial lung disease. Respirology 2012;17(3):525-532.
21. Spiegel D, Sands S, Koopman C. Pain and depression in patients with cancer. Cancer 1994;74(9):2570-2578.
22. Brown GK, Nicassio PM, Wallston KA. Pain coping strategies and depression in rheumatoid arthritis. J Consult Clin Psychol 1989;57(5):652-657.
23. Wrosch C, Scheier MF. Personality and quality of life: the importance of optimism and goal adjustment. Qual Life Res 2003;12 Suppl 1:59-72.
24. Geers AL, Wellman JA, Helfer SG, Fowler SL, France CR. Dispositional optimism and thoughts of well-being determine sensitivity to an experimental pain task. Ann Behav Med 2008;36(3):304-313.
25. Kurtz ME, Kurtz JC, Given CW, Given BA. Patient optimism and mastery-do they play a role in cancer patients' management of pain and fatigue? J Pain Symptom Manage 2008;36(1):1-10.
26. Fournier M, De Ridder D, Bensing J. Optimism and adaptation to chronic disease: The role of optimism in relation to self-care options of type 1 diabetes mellitus, rheumatoid arthritis and multiple sclerosis. Br J Health Psychol 2002;7(Part 4):409-432.
27. McBain H, Shipley M, Newman S. The Impact of Appearance Concerns on Depression and Anxiety in Rheumatoid Arthritis. Musculoskeletal Care 2013 Mar;11(1):19-30.
28. van Hoogmoed D, Fransen J, Bleijenberg G, van Riel P. Physical and psychosocial correlates of severe fatigue in rheumatoid arthritis. Rheumatology (Oxford) 2010;49(7):1294-1302.

CHAPTER 11

HEALTH RELATED QUALITY OF LIFE AND FUNCTIONAL ABILITY IN PATIENTS WITH EARLY ARTHRITIS DURING REMISSION STEERED TREATMENT – RESULTS OF THE IMPROVED-STUDY

Accepted for publication in Arthritis Research & Therapy

L. Heimans, K.V.C. Wevers-de Boer, K.K.M. Koudijs, K. Visser,
Y.P. Goekoop – Ruiterman, J.B. Harbers, G.M. Steup – Beekman, L.R. Lard,
B.A.M. Grillet, T.W.J. Huizinga, C.F. Allaart

ABSTRACT

Purpose: 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: 610 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+pred nisone (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.

Conclusion: 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-alpha 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 and the European League Against Rheumatism (ACR/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 center 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/wk, hydroxychloroquine (HCQ) 400mg/day, sulphasalazine (SSZ) 2000mg/day and prednisone 7.5mg/day (arm 1) or a combination of adalimumab (ADA) 40mg/2weeks and MTX 25mg/wk (arm 2). When patients did not achieve remission after 8 months, patients in arm 1 switched to ADA+MTX and patients in arm 2 increased ADA to 40mg/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, theoutside of protocol subgroup (the 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 antibody (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-analyzed the association with remission defined according to the provisional Boolean based, remission definition published by the American College of Rheumatology and the European League Against Rheumatism (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 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 (ADA+MTX). Fifty patients did not achieve remission but were not randomized (outside of protocol subgroup).[6] Patients who achieved early remission had

lower mean baseline DAS, lower values of all DAS-components, had shorter symptom duration, included fewer females and more patients positive for ACPA (table 1).[5]

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 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 -0.005, 95%CI -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 and 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. Baseline characteristics of all patients.

Baseline characteristics	Early remission n = 387	Arm 1 n = 83	Arm 2 n = 78	OP group 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), median (IQR)	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

Data are presented as means and standard deviations (SD), medians and interquartile ranges (IQR), or numbers and percentages (%). OP group: outside of protocol group, ACPA: anti-citrullinated protein antibody, RA2010: rheumatoid arthritis according to the 2010 ACR/EULAR classification criteria[22], DAS: disease activity score, HAQ: Health Assessment Questionnaire, MCS: Mental Component Score, PSC: Physical Component Score, MACTAR: McMaster-Toronto Arthritis Patients Preference Questionnaire VAS: visual analogue scale.

(table 1 and 2). The mean change in MACTAR in year 1 was not significantly different between arm 1 and 2 (mean difference -1.1, 95%CI -5.2;3.1). The outcomes of the OP group were comparable with those in arms 1 and 2.

Table 2. PROs of all patients over 1 year follow up.

Patient characteristics	Early remission n = 387	Arm 1 n = 83	Arm 2 n = 78	p*	OP group n=50
4 months					
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					
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					
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 (11.2)
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)

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, RA2010: rheumatoid arthritis according to the 2010 American College of Rheumatology classification criteria, DAS: disease activity score, HAQ: Health Assessment Questionnaire, MCS: Mental Component Score, PSC: Physical Component Score, MACTAR: McMaster-Toronto Arthritis Patients Preference Questionnaire VAS: visual analogue scale.
* p-value of the difference in mean scores and remission rates between arm 1 and 2.

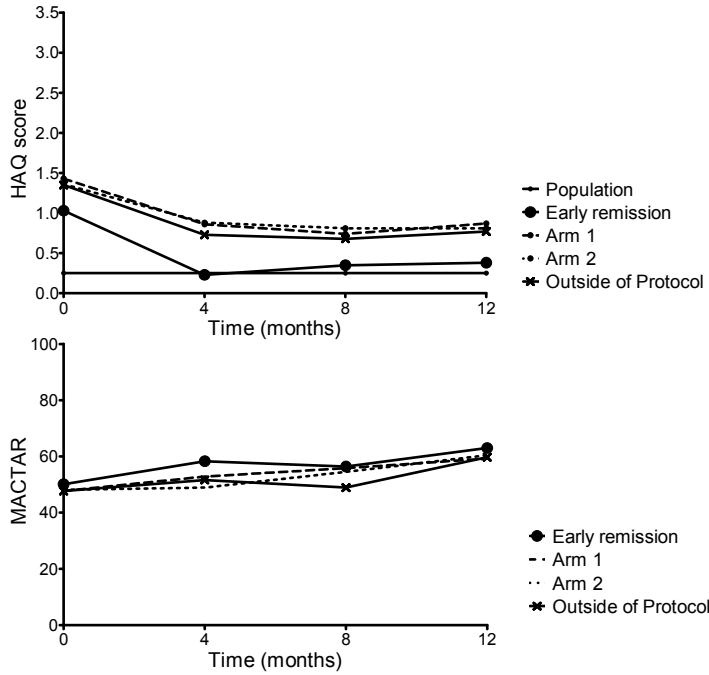

Figure 1. Functional ability as measured by the Health Assessment Questionnaire (HAQ) and the McMaster-Toronto Arthritis Patients Preference Questionnaire (MACTAR). Scores in the first year in the general population (only for HAQ), the early remission group, arm 1, arm 2 and the outside of protocol group.

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 and 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 and 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 the first 4 months and stabilized, but below the population average (table 2 and figure 2). The mean 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 (SD 11.7), in arm 1 8.0 (10.9) and in arm 2 10.1 (12.8). The mean

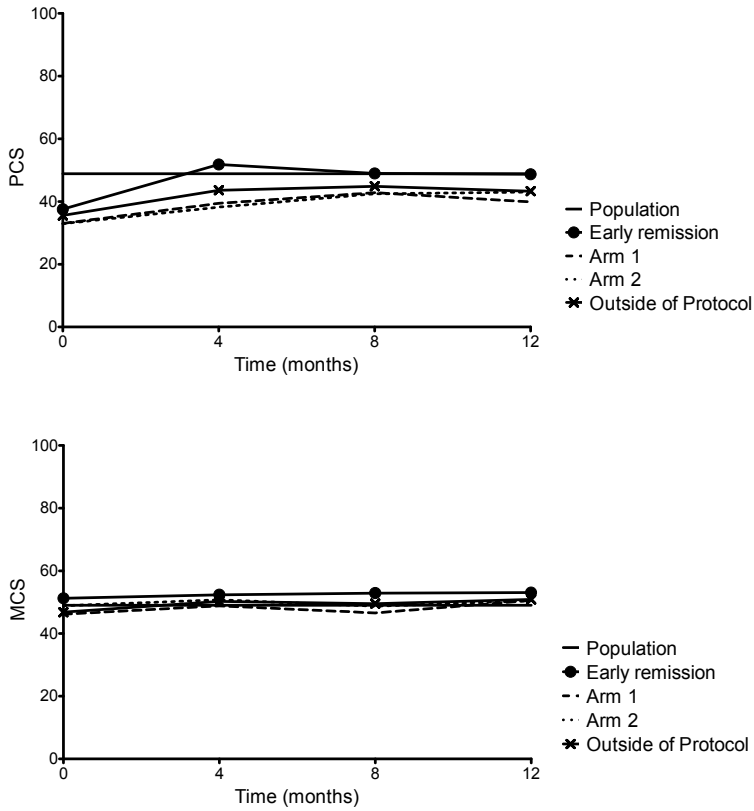

Figure 2. Summary components scores of health as measured by the Short-Form 36 (SF-36). The mental component score (MCS) and the physical component score (PCS), can be calculated from the 8 domains (physical functioning, role limitations due to physical functioning, bodily pain, general health, vitality, social functioning, role limitations due to emotional functioning and mental health) of the SF-36.[12, 13]

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 -2.7, 95%CI -4.9;0.5). There was no significant difference between arm 1 and 2 (mean difference -2.1, 95%CI -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 and 2). Patients in arm 2 reported lower VAS scores than patients in arm 1 after 1 year (table 2). Only for VASda there was more improvement after 1 year in arm 2 than in arm 1 (mean difference 13, 95%CI 2;23) and for the other VAS scores the improvement was comparable between

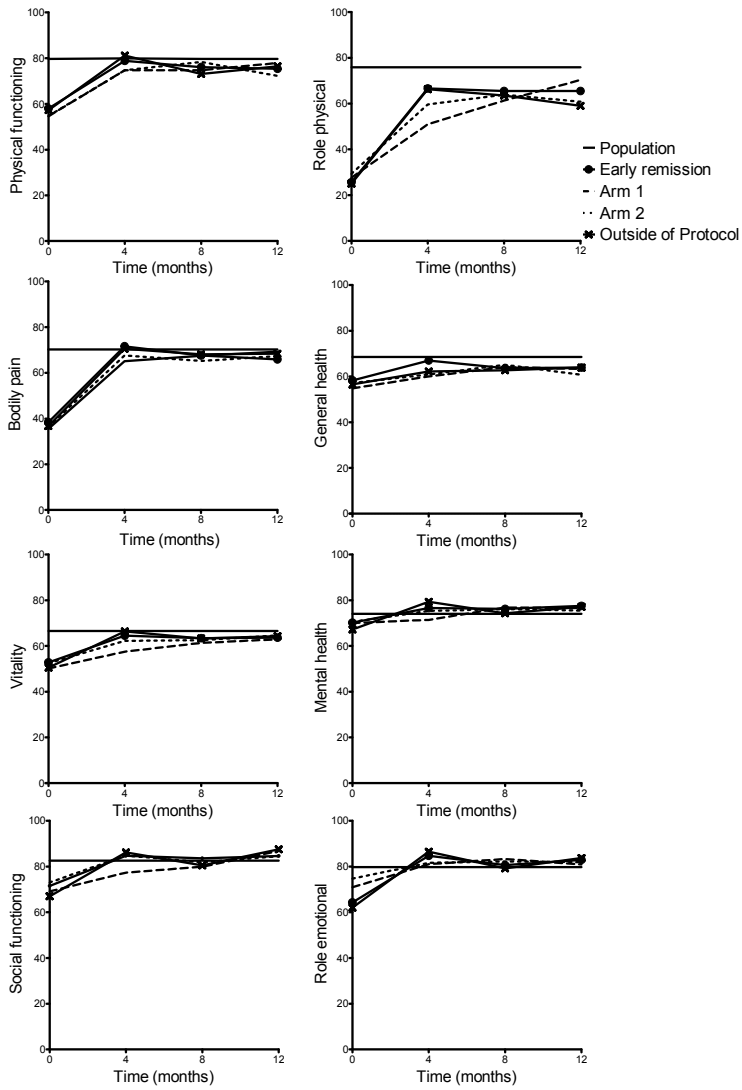

Figure 3. The 8 domains of health as measured by the Short-Form 36 (SF-36; physical functioning, role limitations due to physical functioning, bodily pain, general health, vitality, social functioning, role limitations due to emotional functioning and mental health). The total score ranges from 0 (worst) to 100 (best).

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).

As fixed effects were entered: time (study visit at 4 months, 8 months and 1 year) and mean baseline score of the assessed PRO. The analyses were also performed with adjustment (adjusted beta) 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, these were also entered as fixed variables. For HAQ and PCS there was stratification for treatment group (early remission, arm1, arm 2, outside of protocol group) because of a significant interaction between treatment group and achieving remission.

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

Table 3. Association between the patient reported outcomes and remission achievement during 1 year follow up

	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)	-	-	-	-

OP: outside of protocol group, CI: confidence interval, HAQ: Health Assessment Questionnaire, MACTAR: McMaster-Toronto Arthritis Patients Preference Questionnaire, PCS: Physical Component Score, MCS: Mental Component Score.

with prednisone or 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', functional ability and quality of life comparable with 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 the 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 the 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 the 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 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 disease activity score, rather than having a score just above or below the threshold of remission, may be the main determinant of PRO outcomes. The patients in the outside of protocol subgroup have similar results as patients in arm 1 and 2 which can be explained by the comparable response on initial treatment.

In conclusion, in patients with early (rheumatoid) arthritis, there is an association between achieving remission and having better functional ability and health related quality of life and other PROs, 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.

REFERENCE LIST

1. van der Kooij SM, de Vries-Bouwstra JK, Goekoop-Ruiterman YP et al. Patient-reported outcomes in a randomized trial comparing four different treatment strategies in recent-onset rheumatoid arthritis. Arthritis Rheum 2009;61(1):4-12.
2. Welsing PM, van Gestel AM, Swinkels HL, Kiemeney LA, van Riel PL. The relationship between disease activity, joint destruction, and functional capacity over the course of rheumatoid arthritis. Arthritis Rheum 2001;44(9):2009-2017.
3. Welsing PM, Landewe RB, van Riel PL et al. The relationship between disease activity and radiologic progression in patients with rheumatoid arthritis: a longitudinal analysis. Arthritis Rheum 2004;50(7):2082-2093.
4. Aletaha D, Neogi T, Silman AJ et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010;69(9):1580-1588.
5. Wevers-de Boer K, Visser K, Heimans L et al. Remission induction therapy with methotrexate and prednisone in patients with early rheumatoid and undifferentiated arthritis (the IMPROVED study). Ann Rheum Dis 2012;71(9):1472-1477.
6. Heimans L, Wevers-de Boer KV, Visser K et al. A two-step treatment strategy trial in patients with early arthritis aimed at achieving remission: the IMPROVED study. Ann Rheum Dis 2013.
7. Siegert CE, Vleming LJ, Vandenbroucke JP, Cats A. Measurement of disability in Dutch

rheumatoid arthritis patients. Clin Rheumatol 1984;3(3):305-309.

8. Krishnan E, Sokka T, Hakkinen A, Hubert H, Hannonen P. Normative values for the Health Assessment Questionnaire disability index: benchmarking disability in the general population. Arthritis Rheum 2004;50(3):953-960.
9. Tugwell P, Bombardier C, Buchanan WW, Goldsmith CH, Grace E, Hanna B. The MACTAR Patient Preference Disability Questionnaire--an individualized functional priority approach for assessing improvement in physical disability in clinical trials in rheumatoid arthritis. J Rheumatol 1987;14(3):446-451.
10. Verhoeven AC, Boers M, van der Liden S. Validity of the MACTAR questionnaire as a functional index in a rheumatoid arthritis clinical trial. The McMaster Toronto Arthritis. J Rheumatol 2000;27(12):2801-2809.
11. Boers M, Verhoeven AC, Markusse HM et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet 1997;350(9074):309-318.
12. Aaronson NK, Muller M, Cohen PD et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol 1998 Nov;51(11):1055-68.
13. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992 Jun;30(6):473-83.
14. Kosinski M, Zhao SZ, Dedhiya S, Osterhaus JT, Ware JE, Jr. Determining minimally important changes in generic and disease-specific health-related quality of life questionnaires in clinical trials of rheumatoid arthritis. Arthritis Rheum 2000;43(7):1478-1487.
15. Felson DT, Smolen JS, Wells G et al. American College of Rheumatology/European League against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Ann Rheum Dis 2011;70(3):404-413.
16. Kekow J, Moots R, Khandker R, Melin J, Freundlich B, Singh A. Improvements in patient-reported outcomes, symptoms of depression and anxiety, and their association with clinical remission among patients with moderate-to-severe active early rheumatoid arthritis. Rheumatology (Oxford) 2011;50(2):401-409.
17. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): A randomized, controlled trial. Arthritis Rheum 2008;58(2 Suppl):S126-S135.
18. Hallert E, Husberg M, Skogh T. Costs and course of disease and function in early rheumatoid arthritis: a 3-year follow-up (the Swedish TIRA project). Rheumatology (Oxford) 2006;45(3):325-331.
19. Neovius M, Simard JF, Klareskog L, Askling J. Sick leave and disability pension before and after initiation of antirheumatic therapies in clinical practice. Ann Rheum Dis 2011;70(8):1407-1414.
20. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF et al. Patient preferences for treatment: report from a randomised comparison of treatment strategies in early rheumatoid arthritis (BeSt trial). Ann Rheum Dis 2007;66(9):1227-1232.
21. Marshall NJ, Wilson G, Lapworth K, Kay LJ. Patients' perceptions of treatment with anti-TNF therapy for rheumatoid arthritis: a qualitative study. Rheumatology (Oxford) 2004;43(8):1034-1038.

CHAPTER 12

SUMMARY AND CONCLUSION

Over the past decades it has become clear that treatment of patients with rheumatoid arthritis (RA), preferably combination therapy, has to be initiated in a tight-controlled regimen as soon as possible after diagnosis.[1] This, in order to restore and maintain functional ability and prevent joint damage (progression). Also, health related quality of life and the severity of depressive symptoms seem to improve when patients achieve (early) remission.[2,3] In addition, it may be possible to reverse the disease process altogether and achieve drug free remission (DFR) if effective treatment is initiated very early.

Undifferentiated arthritis (UA) can have a self-remitting course or progress to RA. In the last situation, UA is considered to be an early phase of RA. For these patients, initiation of antirheumatic treatment is suggested, not only for symptom relief but to prevent progression to RA and even aim for a reversal of disease mechanisms.[4,5] It has been shown that methotrexate (MTX), the anchor drug in RA, postpones progression to RA in patients with UA who have anti-citrullinated protein antibodies, but for UA patients without these autoantibodies MTX appears to be as effective as placebo.[6] It has therefore been hypothesized that also for patients with UA, initial combination therapy might be more effective than initial MTX monotherapy to prevent progression to RA, induce (drug free) remission and generally improve disease outcomes.

This thesis focuses on treatment strategies and disease outcomes of patients with RA and UA, based on results of three intervention studies. In *chapter 1* a general introduction on RA, UA, treatment strategies and disease outcomes is given. In the following chapters several studies on these subjects are described; the long term disease outcomes of UA patients in the PROMPT study (*chapter 2*), outcomes during 2 years follow-up in the IMPROVED-study (*chapter 3-5*), subanalyses on treatment response in the IMPROVED-study and the BeSt study (*chapter 6 and 7*), radiological outcomes (*chapter 8 and 9*) and patient reported outcomes, again in the IMPROVED-study (*chapter 10 and 11*).

RA VERSUS UA

In the PROMPT study, patients with UA were treated with initial MTX or placebo. After 30 months it was shown that MTX can postpone, but not prevent, progression from UA to RA.[6] In *chapter 2* of this thesis the long-term outcomes of the PROMPT cohort, after 5 years follow-up, are reported. Patients initially treated with MTX progressed as often to RA (defined according to the 1987 ACR/EULAR classification criteria[7]) as patients initially treated with placebo. Also, joint damage progression was comparable between patients treated with MTX and those treated with placebo, as was the percentage of patients who achieved DFR. Only patients positive for anti-citrullinated protein antibody (ACPA) benefitted from treatment with MTX. However, joint damage progression was more severe in ACPA positives regardless of treatment with MTX or placebo. The main conclusion was that there is hardly any lasting benefit of a one year course of MTX treatment after 5 years, which suggests that early temporary treatment with MTX cannot alter the disease course in UA. This may be due to either the timing and duration of treatment or, the choice of initial treatment.

In retrospect, 39% of the patients could have been classified as RA according to the 2010 classification criteria at baseline, which were formulated to facilitate earlier recognition of RA than with the old (1987) criteria. The new criteria suggest that early treatment may be started because there is a sufficient risk of persistence of symptoms and structural damage.[8] However, for some of these patients the opportunity to change the disease course might have been lost already because of the long duration of symptoms before initiation of treatment. On the other hand, the 2010 classification criteria may also recognize self-limiting types of arthritis as RA. Twenty-five percent of the PROMPT patients who fulfilled the 2010 criteria achieved remission after treatment with placebo. Besides initiating treatment too late, it is possible that discontinuation of MTX after one year was too early. However, the idea of the PROMPT study was to evaluate the effect of early temporary treatment, as induction therapy aiming at remission or at least prevention of progression.

It is possible that MTX monotherapy was not the optimal treatment choice to achieve these goals. MTX is usually the DMARD of first choice in treatment of RA and has been called the anchor drug of antirheumatic treatment. However, it has been shown that initial combination therapy of MTX with corticosteroids or with a biologic DMARD leads to better outcomes in patients with RA.[9-15] In the PROMPT study, 63% of the UA patients who could be reclassified as having RA according to the 2010 classification criteria, still progressed to RA according to the 1987 classification criteria despite treatment with MTX. It may be that with initial combination treatment this could have been prevented.

These considerations were taken on board when the IMPROVED-study was designed. One of the goals of the IMPROVED-study was to compare disease outcomes between patients with RA and patients with UA, the results of which are described in *chapters 3, 4 and 5*. Patients with RA according to the 2010 classification criteria and a symptom duration of less than 2 years, as well as UA patients were included if they showed any disease activity (at least one swollen joint and one other painful joint). All patients were initially treated with combination therapy consisting of MTX and a tapered high dose of prednisone. Subsequent treatment adjustments when remission was not achieved, were required. It was hypothesized that the UA patients would benefit more from the treatment in IMPROVED than the RA patients, presuming they were in an earlier phase of the disease or, alternatively, they had self-limiting disease. On the other hand, it may be that UA patients, with non-RA arthritis, would not respond well to intensive antirheumatic treatment.

After the first four months of treatment (*chapter 3*) the remission rates between patients with RA and UA were comparable (61% versus 65%). After 1 year (*chapter 4*) and after 2 years (*chapter 5*) there were still no differences in remission rates between patients with RA and UA. This, despite the fact that RA patients had a higher disease activity at baseline and were more often positive for ACPA, usually associated with worse disease outcomes.[16] However, in the IMPROVED-study we found that ACPA positivity was one of the strongest predictors for remission at 4 months. In addition, the expectation that UA patients would be in an earlier phase of the disease was refuted by the finding that

symptom duration at baseline was comparable with a median duration of 18 weeks in RA en 16 weeks in UA. This could indicate that we missed the 'window of opportunity', the possibility to modulate the disease process with initiation of treatment before 12 weeks symptom duration,[17] in both RA and UA patients and therefore the opportunity to alter the disease course. However, at year 1 and also at year 2, UA patients were found to have achieved DFR more often than RA patients (*chapter 4 and 5)*. These results suggest that although it is possible to achieve remission in comparable rates, the possibility to taper and stop medication when remission is achieved, is not. Perhaps this difference is related to the significantly lower baseline disease activity in UA patients and the majority of patients not having ACPA.[18]

REMISSION AND DRUG FREE REMISSION

The IMPROVED-study is one of the first studies to steer at remission in patients with early RA and the first to taper and stop medication as soon and as long as patients are in remission. After 4 months of initial treatment with MTX and a tapered high dose of prednisone, 61% of the patients in the IMPROVED-study achieved early remission (*chapter 3)*. After 1 year the remission rate was 54% (*chapter 4*) and 49% after 2 years (*chapter 5*).

Especially the early remission rate (after the first 4 months) of more than 60%, is quite high. This is possibly related to the early initiation of treatment with a proven effective combination of antirheumatic drugs, when symptom duration was relatively short and disease activity not too far from the treatment goal of remission.[19] In addition, some patients with UA and even some patients with early RA might have had a self-limiting type of disease.[5] Also the radiological results are better than previously reported in patients with early RA.[12, 13, 20, 21] For example, 7-33% of the patients in the BeSt study showed progression after 1 year and 20-47% of the patients in the NEO-RACo study showed progression after 2 years.[12, 22] However, the overall remission rates in the IMPROVED-study are only slightly higher than what we observed in the BeSt study.[12, 23] At baseline, those patients had active RA (1987 criteria[7]) with high disease activity, more ACPA positive patients and longer symptom duration. Furthermore, only half of the BeSt study population received initial combination therapy and the target of treatment was low disease activity (DAS≤2.4) instead of remission (DAS<1.6).

Remission, so easily not achieved due to reported pain or elevated ESR due to other causes than RA activity, may be not as readily achieved as low disease activity. It may be that treatment tapering and discontinuation came too early, resulting in loss of remission where it otherwise might have been consolidated. It is also possible that remission was not achieved more often because we missed the 'window of opportunity' in the IMPROVED-study. Because the median symptom duration before inclusion in our patients was 18 weeks, earlier initiation of treatment could have induced higher remission rates, at least in some patients. However, we compared the outcomes of patients with a symptom duration <12 or ≥12 weeks and found no differences. It appears that the initial

treatment with a combination of MTX and prednisone followed by remission steered treatment adjustments is effective, regardless of symptom duration.

Although actual long term remission was not achieved in as many patients as we had hoped, remission steered treatment has resulted in very low disease activity over time in most patients and almost total suppression of joint damage progression across the study population.

INITIAL COMBINATION THERAPY, FOLLOWED BY….?

If, in the IMPROVED-study, the initial combination of MTX and tapered high dose of prednisone was not able to induce remission it was more difficult to achieve remission with the subsequent treatment steps (*chapter 4 and 5)*. Patients who achieved early remission after 4 months were more often in remission and in DFR after 2 years than patients who had not achieved early remission and had been randomized to 2 treatment strategies. Initially, after 1 year, an early switch from the initial combination of MTX and prednisone to MTX with adalimumab resulted in more remission than first expanding treatment with sulphasalazine (SSZ) and hydroxychloroquine (HCQ) (*chapter 4*). This was due to more patients losing remission after tapering the combination of DMARDs with prednisone to MTX monotherapy and fewer patients achieved remission after switching from the combination of MTX, SSZ, HCQ and prednisone to MTX with adalimumab. This last finding reflects data from the BeSt study, where infliximab with MTX was less effective in patients who had first failed on MTX, SSZ and HCQ or leflunomide, than in patients who received infliximab with MTX as initial treatment.[24]

After 2 years (*chapter 6*) the two treatment arms resulted in similar percentages of (drug free) remission with good preservation of functional ability and hardly any radiological damage progression. This may be the effect of continued remission steered treatment adjustments with overlap in treatment and prolonged low disease activity that obscures initial short-term differences. This was also shown in other studies with patients who, after failing on MTX monotherapy, were treated with non-biologic DMARDs or with MTX and a biologic agent.[21, 25, 26]

ACPA

In the PROMPT study (*chapter 2*) there were differences in outcomes between ACPA positive and ACPA negative patients. Time to progression to RA was significantly shorter in ACPA positive patients than in ACPA negative patients and APCA positive patients showed more radiological damage progression. MTX was effective in ACPA positive patients in so far that MTX postponed progression to RA, but did not affect the outcome of ACPA negative patients. The absence of ACPA was the only independent predictor of DFR after 5 years.

Independent predictors of early remission in the IMPROVED-study (*chapter 3)* were low baseline disease activity, low numbers of painful and/or swollen joints, male sex, lower body mass index (BMI) and ACPA positivity. ACPA has always been associated with a worse

response and disease outcome and therefore it was not expected that ACPA positivity would be a predictor of early remission but there are explanations for this finding.[18, 27] The 2010 classification criteria for RA depend on a score that is based on presence and severity of arthritis on examination and presence and titer of autoantibodies. Patients with a low score for arthritis will still be classified as RA if high autoantibody (ACPA, rheumatoid factor) titers are present, patients without autoantibodies require a large number of inflamed joints to be classified as RA. Patients not meeting the classification criteria (UA patients) only have a few inflamed joints and they are almost all ACPA negative. They may have a different type of disease that does not respond as well to the initial combination therapy as classified RA patients. ACPA positive RA patients had less joint involvement than ACPA negative RA patients, and consequently, the ACPA negative RA patients in the IMPROVED-study had a higher disease activity (and they also had a longer symptom duration). These differences may explain why ACPA negative patients achieved less remission after 4 months than ACPA positive patients.

After 1 year 32% of the patients in the IMPROVED-study achieved drug free remission (DFR_{1year}) and in 65% of those, DFR was sustained for at least 4 more months (*chapter 6*). Presence of RF, classified RA (2010 classification criteria) and a low tender joint count at baseline were associated with achieving DFR_{1year} but none was independently associated with $DFR_{1year.}$ Notwithstanding the results after 4 months, ACPA positive patients achieved DFR as often as ACPA negative patients, but ACPA positive patients less often had sustained DFR. In a previous study, it was reported that absence of ACPA was an independent predictor of sustained DFR.[18] The comparable DFR_{1year} rates in the IMPROVED-study may be explained both by the efficiency of the initial combination of MTX and prednisone and the early start of targeted treatment, steered at remission. Although achieving DFR_{1year} was achieved in comparable percentages of patients, sustaining DFR seems to be a different target. Perhaps, in ACPA positive patients tapering came too soon or we should have initiated a different combination of drugs.

The differences in outcomes between ACPA positive and ACPA negative arthritis may indicate that these are different diseases with different pathogenic mechanisms leading to disease activity. It may be that the effect of treatment depends on which pathogenic mechanisms drive disease activity and that therapy should be started and adjusted according to this. Current lack of knowledge of the molecular mechanisms that drive disease activity may prevent targeted interventions in particular for ACPA negative disease.

REMISSION AND BODY MASS INDEX

Besides ACPA there are other factors that may influence how patients respond to treatment. It was previously reported that patients with a high body mass index (BMI), previously treated with at least two DMARDs, responded less well to treatment with fixed-dose infliximab (IFX).[28] It is speculated that this diminished response in patients with a high BMI may be due to high levels of pro-inflammatory cytokines produced by adipocytes.[29, 30]

In the BeSt study, patients with early RA were randomized to initial MTX monotherapy or initial combination therapy (with MTX, SSZ and prednisone or with MTX and IFX) and the target of treatment was low disease activity (DAS≤2.4).[12] In the BeSt population, high BMI was associated with failure to achieve low disease activity on antirheumatic therapy. The association between high BMI and response to treatment was most noticeable in patients treated with combination therapy and we also found that patients with a high BMI failed more often on IFX, as initial treatment and also if the dosages were increased (*chapter 7)*. Failing was dependent on higher pain and joint tenderness scores.

Presuming that BMI is associated with higher inflammatory activity, one would expect that failure to achieve a DAS≤2.4 in patients with a high BMI would be reflected in increased inflammatory parameters. This we did not find. This may be due to small numbers in our investigation, as there were not many patients with a BMI above 30 kg/m^2. In addition, joint evaluation can be a challenge in patients with a high BMI and it is possible that joint swelling was underestimated. It was previously shown that local joint tenderness is an independent predictor of local joint damage progression,[31] and therefore we cannot rule out that joint tenderness was an indicator of joint inflammation even in the absence of noticeable swelling. However, there were no differences in joint damage progression between patients with high or low to normal BMI, suggesting that high BMI patients with high pain and joint tenderness scores did not have inflammatory activity. It may be that there was a fibromyalgia component responsible for the pain in patients with a high BMI.[32] It is suggested that there are certain hormones and neurotransmitters that are responsible for an association between high BMI and pain.[32] Especially musculoskeletal pain is experienced more often in patients with a BMI above 30 kg/m^2 and often in more than one location[33, 34] Alternatively, the comparable progression rates may be a result of treatment adjustments triggered by high pain and joint tenderness scores, or may reflect a protective effect of BMI on joint damage.[32, 35, 36] Either way, the association between pain and BMI may also explain the decreased functional ability in patients with a high BMI, as it was previously reported that pain as well as body size may interfere with daily activities.[37]

RADIOLOGY

Early treatment and suppression of disease activity leads to better suppression of radiological damage progression.[38-40] Starting treatment early in disease course brings a risk of overtreatment, for instance in patients with self-limiting arthritis, but it also may result in prevention or suppression of joint damage progression.

One of the most significant findings after 2 years remission steered treatment in the IMPROVED-study, is the almost complete suppression of joint damage progression in the vast majority of patients, whether they were in remission or had not met that threshold. Only 50 patients of the original 610 showed progression of at least a 0.5 point increase in Sharp-van der Heijde Score (SHS) after 2 years, and only 8 (1%) had damage progression >5 points, which is considered the minimal clinically relevant difference.[41]

If combination therapy is started early and treatment is steered at achieving remission, then radiological damage progression may be suppressed to the extent that it becomes difficult to score. We scored less erosions after 2 years follow-up than after 1 year (*chapter 5)*. Minimal joint damage is difficult to distinguish from normal variations. Since we scored the radiographs in time random order we were even less likely to score progression, as chronological scoring has been shown to be more sensitive to change.[41,42] Repair as explanation for the lower erosion score is less likely, as this happens mainly in damaged joints.[43] Despite these differences in scoring, the overall outcome remains that radiological joint damage progression was very low, both after 1 and after 2 years.

Rapid radiological progression (RRP), defined as ≥5 points progression in the first year after diagnosis, has been demonstrated to be an early outcome that is associated with a bad prognosis regarding further damage progression and functional disability.[44]A prediction model to identify which patient will develop RRP and may need more extensive treatment has been developed with data from the BeSt study[45] and was tested in the IMPROVED-study (*chapter 8*). The model was not useful to predict damage progression in patients with UA and early RA who participated in the IMPROVED-study.

A matrix model to predict RRP might not be applicable to a study population that showed hardly any damage progression and in only one patient RRP. Baseline disease activity and symptom duration appeared to be lower in the IMPROVED-study than in the BeSt study. In addition, the IMPROVED patients had shorter symptom duration and they all received initial combination therapy with MTX and prednisone, whereas half of the BeSt patients had received initial MTX monotherapy. As a consequence, not only were baseline disease activity lower and symptom duration shorter in the IMPROVED-study, also the risk factors used in the matrix model, were less often present in the IMPROVED patients: CRP values were lower, they were less often erosive at baseline and less often ACPA and/or RF positive.

Thus, RRP was less likely in most IMPROVED patients, and particularly unlikely in the UA patients. Based on the matrix model, 13 patients had an intermediate risk of RRP and only 2 of those showed progression of ≥0.5 SHS in year 1, the others showed no progression. This is possibly related to targeted treatment aiming at remission in the IMPROVED-study, which resulted in suppression of disease activity. One patient, predicted to have low risk actually showed RRP. By treating arthritis patients earlier, with remission targeted therapy, RRP and indeed also minimal radiologic damage progression may be prevented. Prediction models based on data from previous patients populations may thus no longer be relevant for current and future patients. Residual disease activity may still have an effect on cartilage and bone in and around arthritic joints and newer techniques to monitor these effects may need to be employed and next, new risk factors for joint damage may be identified.

Early in the disease course there are subtle changes in the form of metacarpal osteopenia in the bones which are difficult to detect and score by conventional X-rays, the gold standard to evaluate joint damage.[46] Changes in metacarpal bone mineral density (mBMD) can be measured with Digital X-ray Radiogrammetry (DXR). In early RA, loss

of mBMD during the first year after diagnosis is predictive for radiological damage up to 5 years afterwards.[47-50] For clinical practice the predictive value of metacarpal BMD loss would be greater if it can be measured earlier in the disease course. Therefore we measured mBMD loss 4 months after the start of treatment and evaluated if it was a predictor of damage after 1 year. Presence of erosions at baseline and mBMD loss after 4 months were predictive of radiological progression after 1 year (*chapter 9*). In patients without baseline erosions, 86% of the IMPROVED population, mBMD loss after 4 months was the only predictor for future joint damage progression. Thus, measuring mBMD loss after 4 months may help making treatment decisions early in the disease course. As mentioned earlier, only a few patients had radiological damage progression and we acknowledge that the value of DXR has to be validated in other studies as well.

PATIENT REPORTED OUTCOMES

Treatment not only improves disease outcomes in terms of remission and radiological damage progression, but it also influences how patients judge their quality of life.[2] If the treatment target in RA is remission, which can be defined as 'the absence of troublesome disease activity',[51] treatment should result in patients having no symptoms and no limitations or restrictions in functional ability, psychological wellbeing and quality of life. These so-called patient reported outcomes (PROs) can be measured with questionnaires and improving or maintaining them becomes more and more important in arthritis patients.

Depressive symptoms are more common in patients with RA compared to healthy individuals.[3, 52-54] Based on the finding that increased serum levels of cytokines IL-1, IL-6, and Tumour Necrosis Factor alpha (TNF-alpha) were found in patients with depression, it has been hypothesized that the relationship between RA and depression is related to inflammatory processes.[55, 56] In the IMPROVED-study, it appeared that severity of depressive symptoms was associated with achieving remission. This association mainly depended on changes in joint tenderness and self-reported well-being (measured on a visual analogue scale) (*chapter 10*). An association between mood and pain may be bidirectional: pain perception can affect mood, mood can affect pain perception. Patients with higher pain scores at baseline may report more severe depressive symptoms and patients with more severe depressive symptoms may report more pain.[57-59] Non-inflammatory pain can prevent patients from achieving remission and that could explain the higher depression scores. Furthermore, all patients knew that the treatment goal was remission and that medication would be tapered and stopped after achieving remission and it is possible that not achieving the treatment goal also influenced feelings of depression.[3]

All patients were treated with prednisone which can induce extremes in mood like depression and also mania.[60] Because there was no control group, we were unable to evaluate the effect of steroids on mood. On the other hand it is unlikely that prednisone had much effect on depressive symptom severity since none of the patients reported being extremely depressed and the maintenance dose of prednisone was only 7,5mg a day.

As opposed to depressive symptoms which are considered to be a state of mind, optimism is considered a trait and is less variable over time. Indeed, the level of optimism did not significantly change after treatment. However, the increase in 4 months in optimism scores was significantly higher in patients who achieved remission compared to those who did not. This suggests that optimism, as we measured it, is not only a trait and that a part may vary over time and may on some level depend on mood. Optimism and depressive symptoms were associated with each other and perhaps optimistic patients suffered less from depressive symptoms which in turn is related with symptoms like pain and unwell being. Furthermore, optimism is one of the factors that influences coping strategies and could therefore also have an influence on how patients feel; mood but also how fatigued patients are and how much pain they experience.[61-63]

Overall, the severity of depressive symptoms was minimal and optimism scores were only slightly lower than normal. These results were underlined by measurements of mental health related quality of life (HRQoL) measured with the Short-Form 36 (SF-36) (*chapter 11*). Fluctuations were minimal and the scores remained stable around the population average. However, all domains of physical HRQoL were lower than the Dutch population means for healthy individuals who were on average 18 years older[64] and showed a clinically relevant improvement in all patients. This suggests that the impact of early arthritis is mainly physical. Furthermore, it seems that despite the fact that treatment was initiated relatively early and almost nobody had radiological damage at baseline, the disease burden of early arthritis is substantial.

Patients who achieved early remission after 4 months had better PRO outcomes than patients who did not. This may in part be because already at baseline their scores were better. It appears that patients with a milder disease at baseline are predisposed to better disease outcomes and they benefit more from remission steered treatment because they are more likely to achieve scores as are reported by healthy controls. This has a positive influence on ability to work and therefore on personal and societal costs of having (rheumatoid) arthritis.[65, 66]

In the patients who did not achieve early remission and were randomized, PROs remained lower than in the early remission group despite treatment adjustments targeted at remission. In particular functional ability was less and physical HRQoL did not reach the levels found in the general population. After 1 year the PROs between the randomized groups were comparable, although significantly more patients in the MTX plus adalimumab group achieved remission than in the DMARDs plus prednisone group. Only self-reported disease activity was judged better by the patients in the MTX plus adalimumab group, probably because of the significantly lower mean DAS and the higher patient expectations of TNF-alpha inhibitor adalimumab.[67, 68] For all PROs there was an association between achieving remission and an improvement in PRO score. Yet, it is likely that suppression of disease activity in general may be the main determinant of PRO outcomes.

FUTURE PERSPECTIVES AND CONCLUSION

Where the classification criteria in 1987 were meant to identify patients with established RA, the goal of the 2010 criteria is to identify patients who would benefit from early initiation of treatment. Since the publication of the new classification criteria for RA in 2010, the difference between RA and UA has become smaller. Perhaps disease course and outcomes will also become more comparable. In the IMPROVED-study, patients with RA and UA are somewhat different at baseline; RA patients have a higher disease activity and the percentage of ACPA positive patients is higher. The outcomes in both groups, however, are comparable except for the number of patients achieving DFR. On the one side, it is encouraging that RA patients have the same outcomes as UA patients. On the other hand, the ultimate goal of treating patients with UA is trying to change the course of the disease and possibly offer 'a chance for cure' and this appears not to have been achieved.

The comparability of RA and UA stresses the importance of early identification and immediate treatment. But how early is early? According to the 'window of opportunity -theory', 'early' means before 12 weeks symptom duration. However, after 2 years follow-up in the IMPROVED-study there were no differences in the outcomes of patients treated with less or more than 12 weeks symptom duration. This suggests that the 12 weeks threshold which was identified in a RA patients who for the most part were treated with initial monotherapy followed by, at the most, treatment adjustments aiming at low disease activity, may not be relevant if patients are treated with more effective initial combination therapy. However, with early initiation of treatment in patients with UA or even in patients classified as RA, overtreatment is a serious factor to keep in mind.

Also ACPA positivity has previously been identified as a predictor for a poor treatment response and a more severe disease course. ACPA positive and ACPA negative arthritis can almost be considered as different disease entities and ideally, therapy should be started and adjusted according to those differences.[6] In the IMPROVED-study patients were initially treated with MTX and prednisone. We found that after 1 year remission steered treatment, ACPA positive patients achieved remission as often as ACPA negative patients and that in both groups, damage progression was minimal and comparable. The only noticeable difference was that ACPA positive patients were less often able to sustain DFR and after 2 years they less often achieved DFR. These results may indicate that differences in outcomes between patients with a good prognosis and a poor prognosis, become smaller. This can be explained by effective treat-to-target treatment strategies resulting in better outcomes in general and thus in comparable results between patients with and without predictors of a worse disease outcome. It may also indicate that there may be other predictors of outcome yet to be identified. All these results indicate that disease outcomes in early arthritis have been further improved with treatment strategies like those of the IMPROVED-study. Although remission is achieved in a large proportion of patients nowadays, ideally DFR would be achieved in more (or preferably all) patients and for long periods of time. Future study results, including those of the IMPROVED-study, will

have to demonstrate predictors of sustained (drug free) remission. Not only remission rates, but also well-being and quality of life seem to benefit from early initiation of MTX and a tapered high dose of prednisone. Patients reported feeling better with suppression of disease activity, especially when remission was achieved early in the disease course. Because there may be a bidirectional relationship between several PROs and response to treatment, patient care could possibly be further improved with routine assessments of PROs which could be taken into account to make treatment decisions.

In the IMPROVED-study, patients who do not achieve early remission, achieved much lower remission and drug free remission (DFR) rates compared to patients who achieved early remission on initial combination therapy. This, despite continued remission steered treatment adjustments including continued use of low dose prednisone and use of combinations of drugs including multiple non-biologic DMARDs and biologic agents like adalimumab. Perhaps patients respond less well to treatment in case of a relative delay in finding the right treatment or they may have a type of illness that requires different medication altogether. As in some patients there may be a background of augmented perception of pain where stronger anti-inflammatory drugs may not be the answer. Identification of new risk factors for not achieving early remission may be a first step towards tailor-made treatment for these patients.

Without losing sight of the benefits of remission steered treatment as was the basis of the IMPROVED-study, we should also take into account the possible downsides of such a strategy. Early use of adalimumab, or biologic agents in general, comes with high drug costs and potential side effects. Also, the high dose of prednisone and continued use of low dose prednisone in some patients, may come with a risk for infections and other complications. We have recorded all side effects, but without a non-prednisone control group we cannot assess the risk of this treatment. There could be alternatives, with a lower dose of prednisone.[69]

In conclusion, in patients with recent onset RA or UA, remission targeted treatment results in continued high remission rates and drug free remission rates. Patients who achieved remission in an early phase of the disease also achieved more (drug free) remission in the long run. Radiological damage progression was almost completely suppressed. Also, a good response to treatment may prevent chronic deterioration in various patient reported outcomes.

The results in this thesis suggests that, if diagnosed and treated early, RA may not progress to the chronic and destructive autoimmune disease as we knew it. Compared to results in older cohorts, the disease outcomes are better regardless of traditional poor prognostic factors and up to the point that radiological damage on conventional radiographs has become difficult to score and may no longer be clinically relevant. Additional research should focus not only on finding early, effective treatment for those patients who did not achieve early remission on MTX with prednisone, but also on identifying imaging techniques that may be sufficiently sensitive and reliable to use as methods of treatment

evaluation. It should also focus on identifying new prognostic factors that contribute towards more individualized treatment strategies which will make further improvements in the treatment of patients with early arthritis possible in the future.

REFERENCE LIST

1. Grigor C, Capell H, Stirling A et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. Lancet 2004;364(9430):263-269.
2. van der Kooij SM, de Vries-Bouwstra JK, Goekoop-Ruiterman YP et al. Patient-reported outcomes in a randomized trial comparing four different treatment strategies in recent-onset rheumatoid arthritis. Arthritis Rheum 2009;61(1):4-12.
3. Kekow J, Moots R, Khandker R, Melin J, Freundlich B, Singh A. Improvements in patient-reported outcomes, symptoms of depression and anxiety, and their association with clinical remission among patients with moderate-to-severe active early rheumatoid arthritis. Rheumatology (Oxford) 2011;50(2):401-409.
4. Verpoort KN, van Dongen H, Allaart CF, Toes RE, Breedveld FC, Huizinga TW. Undifferentiated arthritis--disease course assessed in several inception cohorts. Clin Exp Rheumatol 2004;22(5 Suppl 35):S12-S17.
5. Harrison BJ, Symmons DP, Brennan P, Barrett EM, Silman AJ. Natural remission in inflammatory polyarthritis: issues of definition and prediction. Br J Rheumatol 1996;35(11):1096-1100.
6. van Dongen H, van Aken J, Lard LR et al. Efficacy of methotrexate treatment in patients with probable rheumatoid arthritis: a double-blind, randomized, placebo-controlled trial. Arthritis Rheum 2007;56(5):1424-1432.
7. Arnett FC, Edworthy SM, Bloch DA et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31(3):315-324.
8. Aletaha D, Neogi T, Silman AJ et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010;69(9):1580-1588.
9. O'Dell JR, Haire CE, Erikson N et al. Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications. N Engl J Med 1996;334(20):1287-1291.
10. Boers M, Verhoeven AC, Markusse HM et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet 1997;350(9074):309-318.
11. Klareskog L, van der Heijde D, de Jager JP et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet 2004;363(9410):675-681.
12. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. Arthritis Rheum 2005;52(11):3381-3390.
13. Breedveld FC, Weisman MH, Kavanaugh AF et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum 2006;54(1):26-37.
14. de Jong PH, Hazes JM, Barendregt PJ et al. Induction therapy with a combination of DMARDs is better than methotrexate monotherapy: first results of the tREACH trial. Ann Rheum Dis 2013 Jan;72(1):72-8.
15. Mottonen T, Hannonen P, Leirisalo-Repo M et al. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. Lancet 1999;353(9164):1568-1573.
16. Visser K, Verpoort KN, van Dongen H et al. Pretreatment serum levels of anti-cyclic citrullinated peptide antibodies are associated with the response to methotrexate in recent-onset arthritis. Ann Rheum Dis 2008;67(8):1194-1195.
17. Quinn MA, Emery P. Window of opportunity in early rheumatoid arthritis: possibility of altering the disease process with early

intervention. Clin Exp Rheumatol 2003;21(5 Suppl 31):S154-S157.

18. van der Woude D, Visser K, Klarenbeek NB et al. Sustained drug-free remission in rheumatoid arthritis after DAS-driven or non-DAS-driven therapy: a comparison of two cohort studies. Rheumatology (Oxford). 2012 Jun;51(6):1120-8.
19. Keystone E, Freundlich B, Schiff M, Li J, Hooper M. Patients with moderate rheumatoid arthritis (RA) achieve better disease activity states with etanercept treatment than patients with severe RA. J Rheumatol 2009;36(3):522-531.
20. Bakker MF, Jacobs JW, Welsing PM et al. Low-dose prednisone inclusion in a methotrexate-based, tight control strategy for early rheumatoid arthritis: a randomized trial. Ann Intern Med 2012 Mar 6;156(5):329-39.
21. O'Dell JR, Mikuls TR, Taylor TH et al. Therapies for active rheumatoid arthritis after methotrexate failure. N Engl J Med. 2013 Jul 25;369(4):307-18.
22. Leirisalo-Repo M, Kautiainen H, Laasonen L et al. Infliximab for 6 months added on combination therapy in early rheumatoid arthritis: 2-year results from an investigator-initiated, randomised, double-blind, placebo-controlled study (the NEO-RACo Study). Ann Rheum Dis 2013 Jun;72(6):851-7.
23. Klarenbeek NB, Guler-Yuksel M, van der Kooij SM et al. The impact of four dynamic, goal-steered treatment strategies on the 5-year outcomes of rheumatoid arthritis patients in the BeSt study. Ann Rheum Dis 2011;70(6):1039-1046.
24. van der Kooij SM, le Cessie S, Goekoop-Ruiterman YP et al. Clinical and radiological efficacy of initial vs delayed treatment with infliximab plus methotrexate in patients with early rheumatoid arthritis. Ann Rheum Dis 2009;68(7):1153-1158.
25. Moreland LW, O'Dell JR, Paulus HE et al. A randomized comparative effectiveness study of oral triple therapy versus etanercept plus methotrexate in early aggressive rheumatoid arthritis: the treatment of Early Aggressive Rheumatoid Arthritis Trial. Arthritis Rheum 2012 Sep;64(9):2824-35.
26. van Vollenhoven RF, Geborek P, Forslind K et al. Conventional combination treatment versus biological treatment in methotrexate-refractory early rheumatoid arthritis: 2 year follow-up of the randomised, non-blinded, parallel-group Swefot trial. Lancet 2012 May 5;379(9827):1712-20.
27. Klarenbeek NB, van der Kooij SM, Guler-Yuksel M et al. Discontinuing treatment in patients with rheumatoid arthritis in sustained clinical remission: exploratory analyses from the BeSt study. Ann Rheum Dis 2011 Feb;70(2):315-9.
28. Klaasen R, Wijbrandts CA, Gerlag DM, Tak PP. Body mass index and clinical response to infliximab in rheumatoid arthritis. Arthritis Rheum 2011;63(2):359-364.
29. Camhi SM, Bray GA, Bouchard C et al. The relationship of waist circumference and BMI to visceral, subcutaneous, and total body fat: sex and race differences. Obesity (Silver Spring) 2011;19(2):402-408.
30. Hotamisligil GS, Arner P, Caro JF, Atkinson RL, Spiegelman BM. Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. J Clin Invest 1995;95(5):2409-2415.
31. Klarenbeek NB, Guler-Yuksel M, van der Heijde DM et al. Clinical synovitis in a particular joint is associated with progression of erosions and joint space narrowing in that same joint, but not in patients initially treated with infliximab. Ann Rheum Dis 2010;69(12):2107-2113.
32. Ursini F, Naty S, Grembiale RD. Fibromyalgia and obesity: the hidden link. Rheumatol Int 2011;31(11):1403-1408.
33. Hitt HC, McMillen RC, Thornton-Neaves T, Koch K, Cosby AG. Comorbidity of obesity and pain in a general population: results from the Southern Pain Prevalence Study. J Pain 2007;8(5):430-436.
34. Pradalier A, Willer JC, Boureau F, Dry J. Pain and obesity. Lancet 1980;1(8177):1090-1091.
35. van der Helm-van Mil AH, van der Kooij SM, Allaart CF, Toes RE, Huizinga TW. A high body mass index has a protective effect on the amount of joint destruction in small joints in early rheumatoid arthritis. Ann Rheum Dis 2008;67(6):769-774.
36. Westhoff G, Rau R, Zink A. Radiographic joint damage in early rheumatoid arthritis is highly dependent on body mass index. Arthritis Rheum 2007;56(11):3575-3582.
37. Backholer K, Wong E, Freak-Poli R, Walls HL, Peeters A. Increasing body weight and risk of limitations in activities of daily living: a systematic review and meta-analysis. Obes Rev 2012 May;13(5):456-68.
38. Finckh A, Liang MH, van Herckenrode CM, de Pablo P. Long-term impact of early treatment on radiographic progression in rheumatoid

arthritis: A meta-analysis. Arthritis Rheum 2006;55(6):864-872.

39. Klarenbeek NB, Guler-Yuksel M, van der Kooij SM et al. The impact of four dynamic, goal-steered treatment strategies on the 5-year outcomes of rheumatoid arthritis patients in the BeSt study. Ann Rheum Dis 2011;70(6):1039-1046.
40. Boers M, Verhoeven AC, Markusse HM et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet 1997;350(9074):309-318.
41. Bruynesteyn K, van der Heijde D, Boers M et al. Determination of the minimal clinically important difference in rheumatoid arthritis joint damage of the Sharp/van der Heijde and Larsen/Scott scoring methods by clinical experts and comparison with the smallest detectable difference. Arthritis Rheum 2002;46(4):913-920.
42. Boini S, Guillemin F. Radiographic scoring methods as outcome measures in rheumatoid arthritis: properties and advantages. Ann Rheum Dis 2001 Sep;60(9):817-27.
43. van der Linden MP, Boja R, Klarenbeek NB, Huizinga TW, van der Heijde DM, van der Helm-van Mil AH. Repair of joint erosions in rheumatoid arthritis: prevalence and patient characteristics in a large inception cohort. Ann Rheum Dis 2010 Apr;69(4):727-9.
44. van den Broek M, Dirven L, de Vries-Bouwstra JK et al. Rapid radiological progression in the first year of early rheumatoid arthritis is predictive of disability and joint damage progression during 8 years of follow-up. Ann Rheum Dis 2012 Sep;71(9):1530-3.
45. Visser K, Goekoop-Ruiterman YP, de Vries-Bouwstra JK et al. A matrix risk model for the prediction of rapid radiographic progression in patients with rheumatoid arthritis receiving different dynamic treatment strategies: post hoc analyses from the BeSt study. Ann Rheum Dis 2010;69(7):1333-1337.
46. Jensen T, Klarlund M, Hansen M et al. Bone loss in unclassified polyarthritis and early rheumatoid arthritis is better detected by digital x ray radiogrammetry than dual x ray absorptiometry: relationship with disease activity and radiographic outcome. Ann Rheum Dis 2004;63(1):15-22.
47. Forslind K, Boonen A, Albertsson K, Hafstrom I, Svensson B. Hand bone loss measured by digital X-ray radiogrammetry is a predictor of joint damage in early rheumatoid arthritis. Scand J Rheumatol 2009;38(6):431-438.
48. Hoff M, Haugeberg G, Odegard S et al. Cortical hand bone loss after 1 year in early rheumatoid arthritis predicts radiographic hand joint damage at 5-year and 10-year follow-up. Ann Rheum Dis 2009;68(3):324-329.
49. Dirven L, Guler-Yuksel M, de Beus WM et al. Changes in hand bone mineral density and the association with the level of disease activity in patients with rheumatoid arthritis: bone mineral density measurements in a multicenter randomized clinical trial. Arthritis Care Res (Hoboken) 2011;63(12):1691-1699.
50. Guler-Yuksel M, Klarenbeek NB, Goekoop-Ruiterman YP et al. - Accelerated hand bone mineral density loss is associated with progressive joint damage in hands and feet in recent-onset rheumatoid arthritis. Arthritis Res Ther. 2010;12(3):R96.
51. Felson D. Defining remission in rheumatoid arthritis. Ann Rheum Dis 2012;71 Suppl 2:i86-i88.
52. Dickens C, McGowan L, Clark-Carter D, Creed F. Depression in rheumatoid arthritis: a systematic review of the literature with meta-analysis. Psychosom Med 2002;64(1):52-60.
53. Covic T, Tyson G, Spencer D, Howe G. Depression in rheumatoid arthritis patients: demographic, clinical, and psychological predictors. J Psychosom Res 2006;60(5):469-476.
54. Pincus T, Griffith J, Pearce S, Isenberg D. Prevalence of self-reported depression in patients with rheumatoid arthritis. Br J Rheumatol 1996;35(9):879-883.
55. O'Brien SM, Scott LV, Dinan TG. Cytokines: abnormalities in major depression and implications for pharmacological treatment. Hum Psychopharmacol 2004;19(6):397-403.
56. Maes M, Bosmans E, De Jongh R, Kenis G, Vandoolaeghe E, Neels H. Increased serum IL-6 and IL-1 receptor antagonist concentrations in major depression and treatment resistant depression. Cytokine 1997;9(11):853-858.
57. Ryerson CJ, Arean PA, Berkeley J et al. Depression is a common and chronic comorbidity in patients with interstitial lung disease. Respirology 2012;17(3):525-532.
58. Spiegel D, Sands S, Koopman C. Pain and depression in patients with cancer. Cancer 1994;74(9):2570-2578.
59. Brown GK, Nicassio PM, Wallston KA. Pain coping strategies and depression in

rheumatoid arthritis. J Consult Clin Psychol 1989;57(5):652-657.

60. Brown ES. Effects of glucocorticoids on mood, memory, and the hippocampus. Treatment and preventive therapy. Ann N Y Acad Sci 2009;1179:41-55.
61. Zenger M, Glaesmer H, Hockel M, Hinz A. Pessimism predicts anxiety, depression and quality of life in female cancer patients. Jpn J Clin Oncol 2011;41(1):87-94.
62. Geers AL, Wellman JA, Helfer SG, Fowler SL, France CR. Dispositional optimism and thoughts of well-being determine sensitivity to an experimental pain task. Ann Behav Med 2008;36(3):304-313.
63. Kurtz ME, Kurtz JC, Given CW, Given BA. Patient optimism and mastery-do they play a role in cancer patients' management of pain and fatigue? J Pain Symptom Manage 2008;36(1):1-10.
64. Aaronson NK, Muller M, Cohen PD et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol 1998 Nov;51(11):1055-68.
65. Hallert E, Husberg M, Skogh T. Costs and course of disease and function in early rheumatoid arthritis: a 3-year follow-up (the Swedish TIRA project). Rheumatology (Oxford) 2006;45(3):325-331.
66. Neovius M, Simard JF, Klareskog L, Askling J. Sick leave and disability pension before and after initiation of antirheumatic therapies in clinical practice. Ann Rheum Dis 2011;70(8):1407-1414.
67. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF et al. Patient preferences for treatment: report from a randomised comparison of treatment strategies in early rheumatoid arthritis (BeSt trial). Ann Rheum Dis 2007;66(9):1227-1232.
68. Marshall NJ, Wilson G, Lapworth K, Kay LJ. Patients' perceptions of treatment with anti-TNF therapy for rheumatoid arthritis: a qualitative study. Rheumatology (Oxford) 2004;43(8):1034-1038.
69. den Uyl D, Ter Wee M, Boers M et al. A non-inferiority trial of an attenuated combination strategy ('COBRA-light') compared to the original COBRA strategy: clinical results after 26 weeks. Ann Rheum Dis. 2013 May 31.

CHAPTER 13

NEDERLANDSE SAMENVATTING

De afgelopen decennia is uit onderzoek gebleken dat patiënten met reumatoïde artritis (RA) zo snel mogelijk na het stellen van de diagnose moeten starten met de behandeling, bij voorkeur met combinatietherapie. Op deze manier kunnen beperkingen in het dagelijks functioneren hersteld worden en kan schade(progressie) aan de gewrichten voorkomen worden. Ook de kwaliteit van leven en de stemming lijken te verbeteren wanneer de ziekteactiviteit snel onder controle is. Daarnaast is het wellicht mogelijk dat, indien de doeltreffende behandeling heel vroeg wordt gestart, het ziekteproces een halt kan worden toegeroepen en medicatievrije remissie wordt bereikt.

Ongedifferentieerde artritis (van het Engelse undifferentiated artritis; UA) kan vanzelf over gaan, maar kan zich ook ontwikkelen tot RA. In het laatste geval wordt UA beschouwd als een vroege fase van RA. Ook bij patiënten met UA wordt een tijdige start met antireumatische medicatie aanbevolen. Niet alleen vanwege de symptoomverlichting maar ook om progressie naar RA te voorkomen, en wellicht zelfs om het ziekteproces te stoppen. Methotrexaat (MTX) is het meest voorgeschreven middel bij patiënten met RA, maar ook patiënten met UA die autoantilichamen genaamd ACPA (anti-citrullinated protein antibodies, geassocieerd met slechtere ziekte-uitkomsten) in het bloed hebben, hebben hier baat bij omdat het de progressie naar RA uitstelt. In UA patiënten zonder deze autoantilichamen blijkt MTX echter net zo effectief als placebo. Dit suggereert dat patiënten met UA wellicht ook meer baat hebben bij initiële combinatietherapie, in plaats van MTX monotherapie, om progressie naar RA te voorkomen, om (medicatievrije) remissie te induceren en om de uitkomsten van de ziekte in het algemeen te verbeteren.

Dit proefschrift richt zich op verschillende behandelstrategieën en uitkomstmaten in patiënten met RA en UA, en is gebaseerd op de resultaten van drie interventiestudies. In *hoofdstuk 1* wordt een algemene inleiding gegeven over RA, UA, verschillende behandelingsstrategieën en relevante uitkomstmaten. In de daaropvolgende hoofdstukken wordt een aantal studies over deze onderwerpen beschreven; de lange termijn uitkomsten van UA patiënten in de PROMPT studie (*hoofdstuk 2*), de uitkomsten van UA en RA patiënten gedurende 2 jaar follow-up in de IMPROVED-studie (*hoofdstuk 3-5*), de respons op de behandeling in de IMPROVED-studie en de BeSt studie (*hoofdstuk 6 en 7*), het voorspellen van radiologische gewrichtsschade in de IMPROVED-studie (*hoofdstuk 8 en 9*), en de visie van de patiënt (de zogenaamde patiënt gerapporteerde uitkomsten) op zijn/haar welbevinden en het effect van de behandeling, opnieuw in de IMPROVED-studie (*hoofdstuk 10 en 11*).

RA VERSUS UA

In de PROMPT studie werden UA patiënten initieel behandeld met MTX of placebo gedurende 1 jaar. Na 30 maanden bleek dat behandeling met MTX de progressie van UA naar RA uitstelde, maar dit niet kon voorkomen. In *hoofdstuk 2* van dit proefschrift worden de lange termijn resultaten van de PROMPT studie, na 5 jaar, besproken. Bij patiënten die initieel behandeld werden met MTX werd even vaak progressie naar RA (gedefinieerd volgens de classificatiecriteria uit 1987 van het American College of Rheumatology (ACR)

en de European League Against Rheumatism (EULAR)) gezien als bij patiënten die werden behandeld met placebo. Ook de hoeveelheid gewrichtsschade was vergelijkbaar tussen patiënten behandeld met MTX en placebo, evenals het aantal patiënten in medicatievrije remissie. Alleen patiënten die positief waren voor ACPA profiteerden van de behandeling met MTX omdat progressie naar RA in deze groep werd uitgesteld. Echter, de gewrichtsschade was ernstiger in deze groep, ongeacht de behandeling met MTX of placebo. De belangrijkste conclusie was dat er na 5 jaar nauwelijks een blijvend effect is van behandeling met MTX in het eerste jaar. Dit suggereert dat vroege, maar tijdelijke behandeling met MTX, het ziektebeloop in patiënten met UA niet kan veranderen. Dit kan zowel het gevolg kan zijn van de timing als van de duur van de behandeling, of de keuze van het geneesmiddel.

Bij enkele patiënten uit de PROMPT studie is het niet gelukt om reeds in een vroeg stadium het ziekteproces af te remmen, waarschijnlijk vanwege de lange duur van symptomen vóór aanvang van de behandeling. Waar alle patiënten volgens de oude (1987) classificatiecriteria nog als UA werden geclassificeerd, kon 39% van deze UA patiënten geclassificeerd worden als RA volgens de in 2010 gepubliceerde classificatiecriteria, die zijn geformuleerd om sneller de diagnose RA te kunnen stellen dan de oude (1987) criteria. Doordat patiënten sneller als RA geclassificeerd worden met deze nieuwe criteria, kan de behandeling ook sneller worden gestart in die patiënten waarbij er een grote kans is op persisterende symptomen en gewrichtsschade. De keerzijde is dat er met de 2010-criteria ook soorten artritis worden geclassificeerd en behandeld als RA, die eigenlijk vanzelf zouden zijn overgegaan; zo bereikte 25% van de PROMPT patiënten die aan de 2010-criteria voldeed remissie na behandeling met placebo.

Naast het '(te) laat' starten van de behandeling is het mogelijk dat het stoppen van MTX na 1 jaar te vroeg was. Echter, het doel van de PROMPT studie was om het effect van vroege, tijdelijke behandeling te onderzoeken.

Het is ook mogelijk dat MTX monotherapie niet de optimale behandeling was om progressie van de ziekte een halt toe te roepen. MTX is doorgaans het middel van eerste keus in de behandeling van RA. Gebleken is dat initiële combinatietherapie bestaande uit MTX en corticosteroïden of MTX met een biologisch antireumatisch medicijn (middelen die bestaan uit dierlijk of menselijk eiwit en het immuunsysteem remmen) leidt tot betere resultaten bij patiënten met RA. In de PROMPT studie trad bij 63% van de UA patiënten die op baseline konden worden geclassificeerd als vroege RA volgens de 2010-criteria, progressie op naar RA (1987) ondanks behandeling met MTX. Mogelijk had dit voorkomen kunnen worden met initiële combinatiebehandeling.

Deze overwegingen zijn meegenomen in het ontwerp van de IMPROVED-studie. Een van de doelstellingen van de IMPROVED-studie was het vergelijken van uitkomsten in patiënten met RA en patiënten met UA. Deze resultaten worden beschreven in *hoofdstuk 3, 4 en 5*. RA werd gedefinieerd volgens de 2010-criteria met een symptoomduur van minder dan 2 jaar. UA werd gedefinieerd als ten minste één gezwollen gewricht en één ander pijnlijk gewricht, onafhankelijk van de symptoomduur. Alle patiënten werden initieel behandeld met

combinatietherapie bestaande uit MTX en hoge dosis prednison die snel werd afgebouwd naar een lagere dosis en vervolgens gecontinueerd werd als onderhoudsdosering. Gedurende de studie werd de behandeling aangepast op basis van de Disease Activity Score (DAS), een berekening van de ziekteactiviteit gemeten met het aantal gezwollen gewrichten en pijnlijke gewrichten, tekenen van ontsteking in het laboratoriumonderzoek en de mening van de patiënt over pijn en welzijn. Een DAS<1,6 geeft aan dat er sprake is van remissie, de afwezigheid van ziekteactiviteit. De hypothese van de IMPROVED-studie was dat de UA patiënten meer baat zouden hebben bij deze behandeling dan patiënten met RA, omdat werd verondersteld dat zij in een vroegere fase van de ziekte zaten en dat sommigen wellicht een ziekte hadden die vanzelf over kon gaan. Anderzijds was het ook mogelijk dat UA patiënten een 'niet als RA herkenbare artritis' hadden en minder goed zouden reageren op een intensieve anti-reumatische behandeling.

Na de eerste vier maanden van de behandeling (*hoofdstuk 3*) waren de remissiepercentages vergelijkbaar tussen patiënten met RA en UA (61% versus 65%). Na 1 jaar (*hoofdstuk 4*) en na 2 jaar (*hoofdstuk 5*) waren er nog steeds geen verschillen. Dit was opvallend omdat RA patiënten een hogere ziekteactiviteit hadden bij aanvang van de studie en vaker ACPA-positief waren, wat doorgaans wordt geassocieerd met een slechtere klinische en radiologische respons. Echter, in de IMPROVED-studie vonden we dat ACPA positiviteit één van de sterkste voorspellers was voor het bereiken van vroege remissie na 4 maanden. Bovendien bleken UA patiënten niet in een veel vroegere fase van de ziekte te zitten want de symptoomduur op baseline was vergelijkbaar tussen RA (18 weken) en UA (16 weken) patiënten. Dit kan erop wijzen dat we de "window of opportunity", de korte tijdspanne van 12 weken waarin het mogelijk lijkt om de uitkomsten van de ziekte gunstig te moduleren indien de behandeling direct wordt gestart, hebben gemist in zowel RA als UA patiënten. Na 1 jaar en ook 2 jaar follow-up bleek dat UA patiënten vaker medicatievrije remissie bereikten dan RA patiënten (*hoofdstuk 4 en 5*). Deze resultaten suggereren dat, hoewel het mogelijk is om in beide groepen evenveel remissie te bereiken, het niet mogelijk is om ook evenveel medicatievrije remissie te bereiken. Een mogelijk verklaring voor dit verschil is de significant lagere ziekteactiviteit op baseline bij UA patiënten en het feit dat de meesten UA patiënten ACPA negatief zijn.

REMISSIE EN MEDICATIEVRIJE REMISSIE

De IMPROVED-studie is één van de eerste studies die de behandeling stuurt op remissie en de eerste studie die medicatie afbouwt en stopt zodra en zolang patiënten in remissie zijn. Na de eerste 4 maanden behandeling met MTX en prednison was 61% van de patiënten (RA en UA) in vroege remissie (*hoofdstuk 3*). Na 1 jaar was 54% van de patiënten in remissie (*hoofdstuk 4*) en na 2 jaar 49% (*hoofdstuk 5*). Vooral het percentage vroege remissie, van ruim 60%, is vrij hoog en te verklaren door de behandeling met een bewezen effectieve combinatie van anti-reumatische geneesmiddelen, de relatief korte symptoomduur, en de ziekteactiviteit die op baseline niet veel hoger was dan het uiteindelijke behandeldoel (namelijk DAS<1,6).

Het is wel merkwaardig dat de remissiepercentages na 1 en 2 jaar follow-up in de IMPROVED-studie slechts iets hoger waren dan de remissiepercentages beschreven in de BeSt studie. De patiënten in de BeSt studie waren gediagnosticeerd met actieve RA (1987 criteria) en hadden een hoge ziekteactiviteit op baseline, waren vaker ACPA positief, en hadden een langere symptoomduur. Bovendien werd slechts de helft van de populatie initieel behandeld met combinatietherapie en was het doel van de behandeling gericht op het behalen van lage ziekteactiviteit (DAS≤2,4) en niet op het behalen van remissie (DAS<1,6), zoals in de IMPROVED-studie. De radiologische schade aan de gewrichten bleek echter wel minder ernstig te zijn in de IMPROVED-studie dan in de Best studie.

Mogelijk is de medicatie in de IMPROVED-studie te vroeg afgebouwd of gestopt, wat resulteerde in verlies van remissie. Een andere verklaring is dat remissie minder vaak dan verwacht werd bereikt omdat we de "window of opportunity" hebben gemist in een deel van de patiënten. Echter, de resultaten van patiënten met een symptoomduur van minder dan 12 weken of met een symptoomduur van 12 weken of meer, waren vergelijkbaar. Dit wijst erop dat initiële behandeling met MTX en prednison gevolgd door remissie gestuurde behandeling effectief is, ongeacht de symptoomduur.

Ondanks dat niet alle patiënten remissie bereiken op de lange termijn, heeft deze remissie gestuurde behandeling wel geleid tot een gemiddeld zeer lage ziekteactiviteit en het vrijwel volledige voorkomen van gewrichtsschadeprogressie.

INITIËLE COMBINATIETHERAPIE, GEVOLGD DOOR...?

Als patiënten in de IMPROVED-studie na 4 maanden geen remissie hadden bereikt met de combinatie van MTX en prednison, dan was het voor deze patiënten moeilijk om met de volgende behandelstappen alsnog remissie te bereiken (*hoofdstuk 4 en 5*). De groep patiënten die vroege remissie bereikten waren na 2 jaar vaker in remissie en in medicatievrije remissie dan patiënten die geen vroege remissie hadden bereikt.

Als patiënten na 4 maanden niet in remissie waren, dan werden zij gerandomiseerd tussen 2 behandelingsstrategieën (uitbreiding met twee disease-modifying antirheumatic drugs (DMARDs) sulfasalazine (SSZ) en hydroxychloroquine (HCQ) of een switch naar MTX+adalimumab). Aanvankelijk, na 1 jaar, resulteerde behandeling met MTX en adalimumab vanaf 4 maanden in een hoger remissiepercentage dan wanneer de initiële behandeling werd uitgebreid met SSZ en HCQ (*hoofdstuk 4*). Daarnaast verloren meer patiënten remissie na het afbouwen van de combinatie van MTX, SSZ, HCQ en prednison naar MTX monotherapie en bereikten minder patiënten remissie na het overstappen van de combinatie van MTX, SSZ, HCQ en prednison naar de combinatie MTX en adalimumab. Deze laatste bevinding weerspiegelt resultaten van de BeSt studie, waarbij infliximab met MTX minder effectief was bij patiënten die eerst hadden gefaald op MTX, SSZ en HCQ of leflunomide, dan bij patiënten die infliximab en MTX als initiële behandeling kregen.

Na 2 jaar (*hoofdstuk 6*) lieten de twee behandelstrategieën soortgelijke percentages (medicatievrije) remissie zien, met een goed behoud van functioneren en nauwelijks radiologische schadeprogressie. Dit kan, in ieder geval deels, verklaard worden door de remissiegestuurde behandeling en de uiteindelijke overlap van de behandeling in de twee armen. Bovendien is het mogelijk dat langdurige lage ziekteactiviteit de verschillen op korte termijn teniet doet. Deze resultaten werden ook gezien in andere studies.

ACPA

De PROMPT studie (*hoofdstuk 2*) liet zien dat er verschillen waren in uitkomsten tussen ACPA positieve en ACPA negatieve patiënten. Progressie van UA naar RA ging significant sneller bij ACPA positieve patiënten en er was meer radiologische schadeprogressie in deze groep. Daarnaast bleek MTX alleen effectief bij ACPA positieve patiënten; progressie van UA naar RA werd alleen in deze groep uitgesteld en MTX had geen effect in ACPA negatieve patiënten. Als laatste werd gevonden dat de afwezigheid van ACPA de enige onafhankelijke voorspeller was voor medicatievrije remissie na 5 jaar.

Onafhankelijke voorspellers voor vroege remissie in de IMPROVED-studie (*hoofdstuk 3*) waren; lage ziekteactiviteit op baseline, weinig pijnlijke en/of gezwollen gewrichten, mannelijk geslacht, lagere 'body mass index' (BMI) en ACPA positiviteit. De laatstgenoemde lag niet in de lijn der verwachting omdat ACPA meestal wordt geassocieerd met slechtere uitkomsten en een slechtere respons op de behandeling. Een verklaring voor deze bevinding kan gevonden worden in de criteria die gesteld zijn voor de classificatie van RA. Volgens de 2010-criteria is de classificatie van RA gebaseerd op de ernst van een artritis en op de aanwezigheid en de titer van autoantilichamen (ACPA en reumafactor (RF)). Patiënten met een milde artritis maar met een hoge titer auto-antilichamen, worden aangemerkt als RA en patiënten zonder autoantilichamen hebben een groter aantal ontstoken gewrichten 'nodig' om te kunnen worden geclassificeerd als RA. De ACPA positieve RA patiënten in IMPROVED hadden inderdaad minder betrokken gewrichten dan ACPA negatieve RA patiënten en als gevolg daarvan hadden de ACPA negatieve RA patiënten een hogere baseline ziekteactiviteit (ze hadden tevens een langere symptoomduur). Dit kan verklaren waarom ACPA negatieve patiënten minder vaak remissie bereikten na 4 maanden dan ACPA positieve patiënten.

Na 1 jaar was 32% van de patiënten in de IMPROVED-studie in medicatievrije remissie en in 65% van deze patiënten hield dit gedurende ten minste 4 maanden stand (*hoofdstuk 6*). Aanwezigheid van RF, geclassificeerde RA (volgens de 2010-criteria), en een laag aantal pijnlijke gewrichten op baseline waren geassocieerd met het bereiken van medicatievrije remissie na 1 jaar. Echter, geen van de variabelen was onafhankelijk geassocieerd met medicatievrije remissie. ACPA positieve patiënten bereikten net zo vaak medicatievrije remissie als ACPA negatieve patiënten, maar ACPA positieve patiënten konden minder vaak in medicatievrije remissie blijven. In een eerdere studie werd al gerapporteerd dat de afwezigheid van ACPA een onafhankelijke voorspeller was voor het behouden van

medicatievrije remissie. Dat in een vergelijkbaar percentage ACPA positieve en ACPA negatieve patiënten medicatievrije remissie bereikt werd in IMPROVED kan verklaard worden door zowel de efficiëntie combinatie van MTX en prednison, en de tijdige start van doelgerichte behandeling. Hoewel vergelijkbare percentages in het behalen van medicatievrije remissie werden gevonden, lijkt het behouden van medicatievrije remissie iets anders. Wellicht hebben ACPA positieve patiënten een andere behandelstrategie nodig dan ACPA negatieve patiënten; bij ACPA positieve patiënten zou misschien minder snel afgebouwd moeten worden of juist gestart met een andere combinatie van medicijnen.

De verschillen in uitkomsten tussen ACPA positieve en ACPA negatieve artritis kunnen erop wijzen dat dit verschillende ziekten zijn met verschillende pathofysiologische mechanismen die leiden tot ziekteactiviteit. Mogelijk is het effect van de behandeling afhankelijk van deze pathofysiologische mechanismen en moet de behandeling worden aangepast aan deze mechanismen. Het huidige gebrek aan kennis van de moleculaire mechanismen die ten grondslag liggen aan ziekteactiviteit maakt dat gerichte interventies, in het bijzonder voor ACPA negatieve ziekte, (nog) niet mogelijk zijn.

REMISSIE EN BMI

Naast ACPA zijn er ook andere factoren die van invloed zijn op de behandelrespons. Uit eerder onderzoek is gebleken dat patiënten met een hoog BMI die eerder behandeld waren met ten minste twee DMARDs, minder goed reageerden op de behandeling met infliximab (IFX). De hypothese die hier aan ten grondslag ligt is dat deze verminderde respons bij patiënten met een hoog BMI verklaard kan worden door een hoog aantal 'ontstekingsbevorderende stoffen' (pro-inflammatoire cytokinen) vanuit vetcellen.

In de BeSt studie werden patiënten met vroege actieve RA behandeld met initiële MTX monotherapie of initiële combinatietherapie (combinatie van MTX, SSZ en prednison of de combinatie van MTX en IFX) waarbij het doel het bereiken van lage ziekteactiviteit (DAS≤2,4) was. In de BeSt populatie bleek een hoog BMI geassocieerd te zijn met het minder vaak bereiken van lage ziekteactiviteit na behandeling (falen), en deze associatie was het meest uitgesproken bij patiënten die behandeld werden met initiële combinatietherapie (*hoofdstuk 7*). Falen, het niet bereiken van lage ziekteactiviteit, was afhankelijk van hogere pijn scores en een groter aantal pijnlijke gewrichten.

Ervan uitgaande dat BMI is geassocieerd met inflammatoire parameters, zou men verwachten dat het niet bereiken van een DAS≤2,4 bij patiënten met een hoog BMI veroorzaakt wordt door verhoogde inflammatoire parameters. De resultaten lieten dit echter niet zien. Dit zou onder andere verklaard kunnen worden door het kleine aantal patiënten met een BMI>30 kg/m^2. Bovendien kan het gewrichtsonderzoek soms een uitdaging zijn bij patiënten met een hoog BMI en daardoor is gewrichtszwelling in deze patiënten mogelijk onderschat. In de BeSt studie werd eerder aangetoond dat pijn in een gewricht een onafhankelijke voorspeller is voor gewrichtsschade in

datzelfde gewricht en daarom is het niet uitgesloten dat gewrichtspijn een indicator is van gewrichtsontsteking, zelfs in de afwezigheid van (objectiveerbare) zwelling. Echter, de mate van gewrichtsschade tussen patiënten met een hoog BMI en een laag/normaal BMI was vergelijkbaar, en dus lijkt het waarschijnlijk dat patiënten met een hoog BMI en veel pijnlijke gewrichten toch geen hogere ontstekingsactiviteit hadden. De vergelijkbare progressie in de verschillende BMI categorieën kan ook het gevolg zijn van gecontinueerde DAS-gestuurde behandeling, waarbij veel pijn leidt tot een hogere score voor ziekteactiviteit en dus een intensievere behandeling. De vergelijkbare gewrichtsschade kan ook verklaard worden door een eerder beschreven beschermend effect van BMI op gewrichtsschade. Mogelijk speelt fibromyalgie een rol in de pijn bij patiënten met een hoog BMI. In de literatuur is beschreven dat bepaalde hormonen en neurotransmitters verantwoordelijk zijn voor een verband tussen een hoog BMI en pijn, en met name musculoskeletale pijn wordt dan vaker aangegeven op meerdere locaties.

De associatie tussen pijn en BMI geeft een ook verklaring voor de verminderde functionele capaciteit bij patiënten met een hoog BMI, daar zowel pijn als lichaamsgrootte kunnen interfereren met de dagelijkse bezigheden.

RADIOLOGIE

Vroege en doelgerichte behandeling, waarmee de ziekteactiviteit onderdrukt wordt, kan radiologische schadeprogressie voorkomen. Wanneer behandeling vroeg in het ziekteproces wordt gestart bestaat er echter wel een risico op overbehandeling, bijvoorbeeld in patiënten met ongedifferentieerde artritis die ook zonder behandeling over was gegaan.

Eén van de belangrijkste bevindingen na 2 jaar remissiegestuurde behandeling in de IMPROVED-studie is het bijna volledig voorkomen van gewrichtsschade in de overgrote meerderheid van de patiënten, los van het feit of deze patiënten in remissie waren of niet. Slechts 51 patiënten (8%), van de oorspronkelijke 610, hadden progressie van minimaal een 0,5 punt in de Sharp-van der Heijde Score (SHS) na 2 jaar en slechts 8 patiënten (1%) hadden progressie van ≥5 punten, gedefinieerd als het minimale klinisch relevante verschil.

Wanneer combinatietherapie vroeg wordt gestart en de behandeling wordt gestuurd op remissie, wordt radiologische schadeprogressie onderdrukt tot het punt dat elke vorm van schade moeilijk te detecteren is en bovendien ook lastig te onderscheiden van normale variatie. In de IMPROVED-studie werden minder erosies gevonden na 2 jaar follow-up dan na 1 jaar (*hoofdstuk 5*). Marginale gewrichtsschade is moeilijk te onderscheiden van normale variaties in het radiologisch beeld. Aangezien de röntgenfoto's in willekeurige volgorde zijn gescoord (en niet in chronologische volgorde), is het lastig om progressie te detecteren. Repair, het helen van reeds ontstane erosies, als verklaring voor het minder aantal gevonden erosies na 2 jaar follow-up is niet heel waarschijnlijk, aangezien dit vooral optreedt in beschadigde gewrichten. Het meest belangrijk is echter dat, ondanks de verschillen de radiologische gewrichtsschade erg laag was, zowel na 1 als na 2 jaar.

Snelle toename van radiologische schade (zogenaamd rapid radiological progression (RRP)), gedefinieerd als ≥5 punten progressie in het eerste jaar na diagnose, is geassocieerd met een slechte prognose met betrekking tot verdere schadeprogressie en de functionele capaciteit. In de BeSt studie is een voorspelmodel ontwikkeld waarmee het risico op RRP kan worden vastgesteld (door middel van erosies op baseline, de mate van ontsteking in het bloed en de aanwezigheid van autoantilichamen)zodat de initiële behandeling kan worden aangepast aan dat risico. Dit model is in de IMPROVED-studie getest (*hoofdstuk 8*) en bleek niet van toepassing op de IMPROVED populatie, waarschijnlijk door verschillen in inclusiecriteria in beide studies.

Baseline ziekteactiviteit bleek lager te zijn en symptoomduur korter in de IMPROVED-studie dan in de BeSt studie. In de BeSt populatie werden alleen RA patiënten geïncludeerd die voldeden aan de 1987 classificatie criteria met een hoge ziekteactiviteit. In de IMPROVED-studie werden patiënten, volgens de huidige aanbevelingen, zo vroeg mogelijk geclassificeerd als RA volgens de 2010-criteria of als UA met een klinische verdenking op vroege RA. Daarnaast werden alle IMPROVED patiënten behandeld met initiële combinatietherapie bestaande uit MTX en prednison, terwijl in BeSt de helft van de patiënten aanvankelijk MTX monotherapie kregen. Niet alleen was de baseline ziekteactiviteit lager en de symptoomduur korter in de IMPROVED-studie, ook de risicofactoren van het matrix model waren minder vaak aanwezig in de IMPROVED patiënten: patiënten hadden lagere CRP waardes, minder vaak erosieve gewrichtsschade op baseline en ze waren minder vaak ACPA en/of RF-positief. Bovendien werd niemand initieel behandeld met MTX monotherapie. Om deze redenen was RRP minder waarschijnlijk in de meeste IMPROVED patiënten en bijzonder onwaarschijnlijk in de UA patiënten.

Gebaseerd op het model hadden 13 patiënten een gemiddeld risico (20% - 50%) op RRP. Van die 13, waren er 2 patiënten met progressie (≥0,5 SHS) in jaar 1, de anderen hadden geen progressie. Waarschijnlijk is dit te verklaren door de behandeling gericht op remissie in de IMPROVED-studie, waardoor de ziekteactiviteit efficiënt wordt onderdrukt. Eén patiënt met een laag risico op RRP volgens het model had na 1 jaar wél RPP. Waarschijnlijk spelen andere risicofactoren voor schadeprogressie, die niet in het model zijn opgenomen, een rol.

Voorspellingsmodellen voor RRP op basis van gegevens van eerdere studies en patiëntenpopulaties uit de tijd van minder strenge behandelstrategieën, lijken niet meer relevant voor de huidige en voor toekomstige patiënten. Omdat in deze groep patiënten nog wel resterende, nauwelijks meetbare, ziekteactiviteit kan zijn en dit invloed kan hebben op het kraakbeen van de gewrichten, zullen nieuwere technieken moeten worden ontwikkeld. Uiteindelijk zal moeten worden gezocht naar nu nog onbekende risicofactoren voor gewrichtsschade.

Naast röntgenfoto's kunnen andere beeldvormende technieken gebruikt worden om het (vroege) effect van ziekteactiviteit op het bot te bekijken. Met Digitale X-ray Radiogrammetry (DXR), een speciale röntgentechniek, kunnen subtiele veranderingen in

de botdichtheid van de middenhandsbeentjes (mBMD) worden gedetecteerd. Verlies van mBMD in het eerste jaar na diagnose blijkt voorspellend te zijn voor radiologische schade na 5 jaar follow-up. Voor de klinische praktijk zou een vroege detectie van veranderingen in de botdichtheid van de waarde kunnen zijn om de behandeling daarop aan te passen. In IMPROVED is de voorspellende waarde van botdichtheidsverlies na 4 maanden behandeling onderzocht en veranderingen in de botdichtheid bleken radiologische schade na 1 jaar te kunnen voorspellen (*hoofdstuk 9*). De aanwezigheid van erosies op baseline was tevens voorspellend voor radiologische schadeprogressie na 1 jaar follow-up. Bij patiënten die geen erosies op baseline hadden (86% van de patiënten), was verlies van de botdichtheid na 4 maanden behandeling zelfs de enige voorspeller voor toekomstige gewrichtsschade. Het meten van botdichtheidsverlies na 4 maanden follow-up lijkt dus waardevol en kan helpen bij de besluitvorming omtrent de behandeling. Echter, zoals eerder vermeld, slechts een paar patiënten in IMPROVED hadden schadeprogressie en de waarde van de DXR zal daarom verder gevalideerd moeten worden in andere studies.

PATIËNT GERAPPORTEERDE UITKOMSTEN

Behandeling heeft niet alleen invloed op het bereiken van remissie en voorkomen van radiologische schadeprogressie, maar beïnvloedt ook hoe patiënten hun kwaliteit van leven beoordelen. Het behandeldoel in de IMPROVED-studie is remissie, wat kan worden gedefinieerd als 'de afwezigheid van hinderlijke ziekteactiviteit'. Daarmee dient de behandeling niet alleen te leiden tot afwezigheid van symptomen, maar ook tot afwezigheid van beperkingen in functioneren, psychische klachten, en tot een toename of herstel van de kwaliteit van leven. Deze zogenaamde patiënt gerapporteerde uitkomstmaten worden gemeten met behulp van vragenlijsten. In de huidige behandeling van patiënten met artritis speelt het verbeteren en/of handhaven van deze uitkomsten een steeds grotere rol. Depressie komt vaker voor bij patiënten met RA in vergelijking met de gezonde populatie. In patiënten met een depressie werden in eerder onderzoek verhoogde waarden gevonden van de cytokinen IL-1, IL-6 en Tumor Necrose Factor (TNF) alfa. Er wordt gesuggereerd dat de associatie tussen RA en depressie verklaard kan worden door deze inflammatoire processen. In de IMPROVED-studie bleek dat patiënten meer depressieve symptomen rapporteerden wanneer geen remissie werd bereikt, wat voornamelijk afhankelijk was van het aantal pijnlijke gewrichten en het gevoel van welzijn (gemeten op een visueel analoge schaal) (*hoofdstuk 10*). De associatie tussen de stemming en pijn werkt waarschijnlijk twee kanten op: pijn kan de stemming beïnvloeden, maar de stemming kan ook de pijnperceptie beïnvloeden. Patiënten met hogere pijnscores op baseline rapporteerden meer depressieve symptomen, waarbij het uiteraard mogelijk is dat de patiënten met meer depressieve symptomen geneigd zijn tot het rapporteren van meer pijn. Pijn die niet gerelateerd is aan een ontsteking kan een hoge DAS veroorzaken en dat kan er toe leiden dat patiënten geen remissie bereiken, wat vervolgens weer kan leiden tot

meer depressieve symptomen. Bovendien was het voor alle patiënten duidelijk dat het behandeldoel remissie was en dat medicatie daarna afgebouwd en zelfs gestopt kon worden. Het niet bereiken van remissie, en dus het niet bereiken van het behandeldoel, kan ook van invloed geweest zijn op de stemming.

In de IMPROVED-studie werden alle patiënten behandeld met prednison, wat extremen kan veroorzaken in stemming zoals depressie maar ook manie. Vanwege het ontbreken van een controlegroep, kan het daadwerkelijke effect van de prednison niet worden geëvalueerd. Het lijkt echter onwaarschijnlijk dat prednison veel effect heeft gehad op de stemming, omdat geen van de patiënten extremen in de stemming heeft gerapporteerd, en de onderhoudsdosis prednison slechts 7,5 mg per dag was.

Als tegenhanger van depressieve symptomen, die fluctueren over de tijd, wordt optimisme beschouwd als een karaktereigenschap die relatief stabiel is over de tijd. In de IMPROVED-studie bleek dat het niveau van optimisme niet significant was veranderd na de eerste 4 maanden behandeling. Zelfs de patiënten die remissie bereikten na 4 maanden hadden geen significant hoger niveau van optimisme dan patiënten die geen remissie bereikten. Dit zou kunnen betekenen dat optimisme, zoals gemeten in deze studie, toch ook over de tijd kan variëren en op een bepaald niveau afhankelijk is van de stemming. In IMPROVED waren optimisme en depressieve symptomen met elkaar geassocieerd; optimistische patiënten hadden minder last van depressieve symptomen die op hun beurt weer geassocieerd zijn met pijn, welbevinden en remissie. Bovendien is optimisme één van de factoren die invloed heeft op coping en het is daarom plausibel dat optimisme op die manier invloed heeft gehad op hoe patiënten zich voelden, op hun stemming, maar ook op de vermoeidheid van patiënten en de hoeveelheid pijn die ze hadden.

Gedurende het eerste jaar van de IMPROVED-studie werden nog meer patiënt gerapporteerde uitkomsten gemeten; de gezondheidsgerelateerde kwaliteit van leven, gemeten met de Short-Form 36 (SF-36), het functioneren in het dagelijks leven (met de health assessment questionnaire (HAQ)), de mate van pijn, ochtendstijfheid en welbevinden, en de eigen inschatting van de ziekteactiviteit (op een visual analogue scale (VAS), een schaal van 0 tot 100 mm) (*hoofdstuk 11*).

Op baseline bleken met name de fysieke domeinen van gezondheidsgerelateerde kwaliteit van leven aangedaan te zijn en gemiddeld een stuk lager te liggen dan in gezonde personen uit de Nederlandse populatie. Ondanks dat de behandeling relatief vroeg werd gestart en bijna geen enkele patiënt radiologische schade had op baseline, bleek de ziektelast van vroege artritis aanzienlijk. In alle patiënten werd na de behandeling een klinisch relevante verbetering gezien.

Patiënten die vroege remissie hadden bereikt, hadden opnieuw betere uitkomsten (gezondheidsgerelateerde kwaliteit van leven, functioneren, pijn, ochtendstijfheid, welbevinden, en de eigen inschatting van de ziekteactiviteit) dan patiënten die geen vroege remissie bereikten. Omdat de scores van patiënten die vroege remissie

behaalden op baseline al beter waren, kan geconcludeerd worden dat patiënten met een mildere ziekte op baseline waarschijnlijk voorbestemd zijn voor betere uitkomsten en daarom hebben ze meer baat bij remissiegestuurde behandeling omdat de patiënt gerapporteerde uitkomsten in deze groep vergelijkbaar zijn met de gezonde populatie. Dit heeft een positieve invloed op het vermogen om te kunnen werken en dus op de persoonlijke en maatschappelijke kosten van het hebben van (reumatoïde) artritis.

Bij de patiënten die geen vroege remissie bereikten en werden gerandomiseerd, waren alle patiënt gerapporteerde uitkomsten lager dan in de vroege remissie groep. Tussen de gerandomiseerde groepen waren de uitkomsten na 1 jaar bijna geheel vergelijkbaar. Alleen de onderdrukking van de ziekteactiviteit werd in de MTX plus adalimumab groep beter beoordeeld, waarschijnlijk vanwege de lagere DAS en de hogere verwachtingen ten aanzien van TNF-alfa antagonist adalimumab.

Uit de IMPROVED-studie blijkt dat alle PROs waren geassocieerd met het bereiken van remissie. Omdat dit effect ook te zien was in de verschillende randomisatie armen is het waarschijnlijk dat onderdrukking van ziekteactiviteit, ook al is het niet tot het niveau van remissie, toch de belangrijkste determinant is van patiënt gerapporteerde uitkomsten.

TOEKOMSTPERSPECTIEVEN EN CONCLUSIE

De classificatiecriteria uit 1987 waren bedoeld om patiënten met gevorderde RA te identificeren. Het doel van de 2010-criteria is om in een vroeg stadium te identificeren welke patiënten mogelijk een progressiever ziektebeloop krijgen en baat hebben bij een gerichte behandeling. Sinds de publicatie van de nieuwe criteria, is het verschil tussen RA en UA kleiner geworden. Daarmee worden het ziektebeloop en de uitkomsten waarschijnlijk ook meer en meer vergelijkbaar. In de IMPROVED-studie waren er enkele verschillen tussen patiënten met RA en UA op baseline; in RA patiënten was de gemiddelde ziekteactiviteit en het percentage ACPA positieve patiënten hoger. De resultaten wat betreft remissie waren in beide groepen vergelijkbaar, met uitzondering van het aantal patiënten dat medicatievrije remissie behaalde. Aan de ene kant is het bemoedigend dat RA patiënten dezelfde uitkomsten hebben als UA patiënten. Anderzijds is het uiteindelijke doel van de behandeling van UA patiënten om te proberen om het beloop van de ziekte zodanig te veranderen dat zij mogelijk genezen kunnen worden. Helaas lijkt dit doel niet bereikt te zijn in de IMPROVED-studie.

De vergelijkbaarheid van de uitkomsten tussen patiënten met RA en UA benadrukt het belang van vroege herkenning en directe behandeling. Maar hoe vroeg is vroeg? Volgens de 'window of opportunity-theorie' betekent vroeg dat de behandeling vóór 12 weken symptoomduur geïnitieerd moet worden. Na 2 jaar follow-up in de IMPROVED-studie bleken er geen verschillen te zijn in de percentages behaalde remissie van de patiënten met meer of minder dan 12 weken symptoomduur. De 12 weken drempel, die is onderzocht in RA patiënten behandeld met initiële monotherapie, hooguit gevolgd

door behandeling gericht op lage ziekteactiviteit, is waarschijnlijk niet meer relevant wanneer patiënten worden behandeld met een efficiëntere initiële combinatietherapie en DAS- en/of remissiegestuurde behandeling. Echter, met de vroege start van de behandeling bij patiënten met UA of zelfs bij patiënten met geclassificeerde RA, is overbehandeling een belangrijke factor om rekening mee te houden. Toch is overbehandeling vaak tijdelijk, omdat bij de meeste patiënten de medicatie afgebouwd en zelfs gestopt kan worden bij een goede klinische respons.

De aanwezigheid van ACPA wordt beschouwd als voorspeller voor een slechte respons op behandeling en een ernstiger ziekteverloop. ACPA positieve artritis en ACPA negatieve artritis kunnen daarom worden beschouwd als verschillende ziekte entiteiten en idealiter moet de behandeling worden gestart en aangepast aan deze verschillen. In de IMPROVED-studie werden patiënten aanvankelijk behandeld met MTX en prednison. Na 1 jaar remissiegestuurde behandeling waren ACPA positieve en ACPA negatieve patiënten even vaak in remissie en de schade progressie was in beide groepen minimaal en vergelijkbaar. Het enige verschil was dat ACPA positieve patiënten minder vaak langere tijd in medicatievrije remissie konden blijven. De verschillen tussen patiënten met een goede prognose (ACPA negatief) en een slechte prognose (ACPA positief) lijken kleiner te worden. Dit kan deels worden verklaard door de dynamische behandelstrategie binnen de IMPROVED-studie, in dit geval remissiegestuurd, die er in het algemeen voor zorgt dat zowel patiënten met een goede prognose als patiënten met een slechte prognose zo snel mogelijk de voor hun meest effectieve behandeling krijgen. Het kan ook betekenen dat andere factoren een rol spelen en dat deze mogelijk nog niet zijn geïdentificeerd. De resultaten in dit proefschrift geven aan dat de ziekteuitkomsten van vroege artritis verder zijn verbeterd door behandelingsstrategieën zoals die in de IMPROVED-studie. Hoewel in de meeste patiënten al wel remissie werd bereikt, is het ideaalbeeld toch dat er ook medicatievrije remissie wordt bereikt in meer (of bij voorkeur alle) patiënten, voor langere tijd. Toekomstige studieresultaten, waaronder die van de IMPROVED-studie, moeten onderzoeken welke factoren voorspellend zijn voor aanhoudende (medicatievrije) remissie.

Ook de kwaliteit van leven en het algemeen welzijn van de patiënten lijken te verbeteren door de vroege start met combinatietherapie, vooral wanneer remissie vroeg in het ziekteproces werd bereikt. Wellicht kan het routinematig monitoren van patiënt gerapporteerde uitkomsten van pas komen in de dagelijkse praktijk en mee worden genomen in behandelbeslissingen.

In de IMPROVED-studie haalden de patiënten die geen vroege remissie (na 4 maanden) bereikt hadden, veel minder vaak remissie en medicatievrije remissie tijdens follow-up. Gecontinueerde remissiegestuurde behandeling lijkt hier dus geen effect op te hebben. Mogelijk is de respons op behandeling minder goed wanneer het langer duurt om het juiste middel of de juiste combinatie van middelen te vinden. Bij sommige patiënten bestaat er een hoge pijnperceptie waar sterkere anti-inflammatoire geneesmiddelen

geen oplossing voor bieden. Identificatie van onbekende risicofactoren voor het niet bereiken van vroegtijdige remissie is een stap in de richting van behandeling op maat.

Zonder de voordelen van remissiegestuurde behandeling uit het oog te verliezen, moeten we ook rekening houden met de mogelijke nadelen. Het starten van adalimumab, of biologische middelen in het algemeen, vroeg in het ziektebeloop gaat gepaard met hoge kosten en mogelijke bijwerkingen. De initiële hoge dosis prednison, weliswaar voortgezet in een lage dosering in sommige patiënten, geeft een verhoogd risico op infecties en andere complicaties. Echter, zonder een non-prednison controlegroep kunnen we het risico van deze behandeling niet goed beoordelen. Wellicht is MTX met een lagere startdosering prednison net zo effectief.

Samenvattend, bij patiënten met vroege RA of UA leidt remissiegestuurde behandeling tot relatief hoge percentages remissie en medicatievrij remissie. Patiënten die remissie bereiken in een vroege fase van de ziekte, bereiken ook vaker (medicatievrije) remissie op de lange termijn. Bijna alle patiënten toonden een goede onderdrukking van radiologische schadeprogressie. Bovendien voorkomt een goede respons op de behandeling verslechtering van verschillende patiënt gerapporteerde uitkomsten, zoals depressie en kwaliteit van leven.

De resultaten in dit proefschrift onderstrepen dat, als de diagnose vroeg wordt gesteld en er direct wordt gestart met de behandeling, RA niet meer de chronische en destructieve ziekte is die het vroeger was. Vergeleken met de resultaten in oudere cohorten zijn de uitkomsten met de huidige behandelstrategieën beter, ongeacht de aanwezigheid van prognostische factoren die traditioneel als slecht te boek staan, tot aan het punt dat radiologische schade op conventionele röntgenfoto's dusdanig moeilijk te scoren is en misschien niet meer klinisch relevant. Toekomstig onderzoek zal zich niet alleen moeten gaan richten op het vinden van vroege, effectieve behandelingsstrategieën voor patiënten die geen vroege remissie bereiken op MTX en prednison, maar ook op het toetsen van beeldvormende technieken die voldoende gevoelig en betrouwbaar zijn om toe te kunnen passen bij de evaluatie van de behandeling. Ook zal er gericht onderzoek gedaan moeten worden naar nieuwe prognostische factoren die bijdragen aan individuele behandelingsstrategieën die de behandeling en uitkomsten van patiënten met vroege artritis nog verder verbeteren in de toekomst.

APPENDIX

ROLE OF THE FUNDING SOURCE

The rheumatologists participating in the Foundation for Applied Rheumatology Research were responsible for the study design and data collection in the IMPROVED-study, the BeSt study and the PROMPT study. The authors were responsible for the data analysis, interpretation of all data, writing the manuscripts and the decision to publish. The IMPROVED-study was supported by AbbVie. The PROMPT study was supported by the Dutch Arthritis Foundation and by the Netherlands Organisation for Scientific Research. The BeSt study was supported by the Dutch College for Health Insurances with additional funding by Janssen Biologics B.V. and Schering Plough B.V.

LIST OF PUBLICATIONS

L. Heimans, A. van Hylckama-Vlieg, F.W. Dekker. Are claims of advertisements in medical journals supported by RCTs? *Neth J Med 2010; 68(1):46-9.*

K.V.C. Wevers-de Boer, K. Visser, L. Heimans, H.K. Ronday, T.H.E. Molenaar, J.H.L.M. van Groenendael, A.J. Peeters, M.L. Westedt, G. Colleé, P.B.J. de Sonnaville, B.A.M Grillet, T.W.J. Huizinga, C.F. Allaart. Remission Induction Therapy with Methotrexate and Prednisone in patients with Early Rheumatoid and Undifferentiated Arthritis (the IMPROVED-study). *Ann Rheum Dis. 2012; 71(9):1472-7.*

L. Heimans*, M. van den Broek*, S. le Cessie, B. Siegerink, N. Riyazi,H. Han, P.J.S.M. Kerstens, T.W.J. Huizinga, W.F. Lems, C.F. Allaart. Association of high body mass index with decreased treatment response to combination therapy in recent-onset rheumatoid arthritis patients. *Arthitis care Res 2013; 65(8):1235-42.* *Both authors contributed equally.

L. Heimans*, K.V.C. Wevers-de Boer*, K. Visser K, R.J. Goekoop, M. van Oosterhout, J.B. Harbers, C. Bijkerk, I. Speyer, P.D.M. de Buck, P.B.J. de Sonnaville, B.A.M. Grillet, T.W.J. Huizinga, C.F. Allaart. A two-step treatment strategy trial in patients with early arthritis aimed at achieving remission: the IMPROVED-study. *Accepted for publication in Annals of the Rheumatic Diseases.* *Both authors contributed equally.

K.V.C. Wevers-de Boer, L. Heimans, T.W.J. Huizinga, C.F. Allaart. Drug therapy in undifferentiated arthritis: a systematic literature review. *Ann Rheum Dis 2013; 72(9):1336-44.*

L. Heimans, K.V.C. Wevers-de Boer, K. Visser, H.K. Ronday, G.M. Steup-Beekman, M. van Oosterhout, T.W.J. Huizinga, E.J. Giltay, R.C. van der Mast, C.F. Allaart. The relationship between disease activity and depressive symptoms severity and optimism-results from the IMPROVED-study. *Clin Rheumatol 2013; 32(12):1751-7.*

J. van Aken*, L. Heimans*, H. Gillet-van Dongen, K. Visser, H.K. Ronday, I. Speyer, A.J. Peeters, T.W.J. Huizinga, C.F. Allaart. Five-year outcomes of probable rheumatoid arthritis treated with methotrexate or placebo during the first year (the PROMPT study). *Ann Rheum Dis 2014; 73(2):396-400.* *Both authors contributed equally.

L. Heimans, K.V.C. Wevers-de Boer, K.K.M. Koudijs, K. Visser, Y.P. Goekoop-Ruiterman, J.B. Harbers, G.M. Steup-Beekman, L.R. Lard, B.A.M. Grillet, T.W.J. Huizinga, C.F. Allaart. Health related quality of life and functional ability in patients with early arthritis during remission steered treatment - results of the IMPROVED-study. *Accepted for publication in Arthritis Research & Therapy.*

K.V.C. Wevers-de Boer, L. Heimans, K. Visser, J. Kälvesten, R.J. Goekoop, M. van Oosterhout, J.B. Harbers, C. Bijkerk, G.M. Steup-Beekman, P.D.M. de Buck, P.B.J. de Sonnaville, T.W.J.Huizinga, C.F. Allaart. Four-month metacarpal bone mineral density loss predicts

radiological joint damage progression after 1 year in patients with early rheumatoid arthritis: exploratoty analyses from the IMPROVED-study. *Accepted for publication in Annals of the Rheumatic Diseases.*

K.V.C. Wevers-de Boer, L. Heimans, K. Visser, A.A. Schouffoer, E.T.H. Molenaar, J.H.L.M. van Groenendael, A.J. Peeters, I. Speyer, G. Collée, T.W.J. Huizinga, C.F. Allaart. Determinants of drug free remission in patients with early rheumatoid or undifferentiated arthritis after one year of remission steered treatment. *Submitted.*

K.V.C. Wevers-de Boer, L. Heimans, K. Visser, J. Kälvesten, J.A.P.M. Ewals, E.T.H. Molenaar, J. Groenendael, A. Peeters, I Speyer, G. Collee, T.W.J. Huizinga, C.F. Allaart. Changes in metacarpal bone mineral density in patients with undifferentiated and early rheumatoid arthritis during one year of remission steered therapy. *Submitted.*

L. Heimans, K.V.C. Wevers-de Boer, H.K. Ronday, G. Collée, P.B.J. de Sonnaville, B.A.M. Grillet, T.W.J. Huizinga, C.F. Allaart. Can we prevent rapid radiological progression in patients with early arthritis? *Submitted.*

L. Heimans, K.V.C Wevers-de Boer, G. Akdemir, Y.P. Goekoop-Ruiterman, E.T. Molenaar, J.B. Harbers, C. Bijkerk, I. Speyer, M. de Buck, P. de Sonnaville, B. Grillet, T.W.J. Huizinga, C.F. Allaart. Outcomes of two years remission steered treatment in early arthritis patients – the IMPROVED-study. *Submitted.*

CURRICULUM VITAE

Lotte Heimans is geboren op 7 juni 1985 te Amsterdam. Na het behalen van haar Atheneum diploma in 2003 aan het Lyceum Sancta Maria te Haarlem, begon zij in 2003 met de studie psychologie aan de Universiteit Leiden. In 2004 behaalde zij haar propedeuse en daarna begon zij aan de studie geneeskunde aan de Universiteit Leiden en in 2010 behaalde zij het arts-examen.

Vanaf december 2010 was zij als arts-onderzoeker verbonden aan de afdeling reumatologie van het Leids Universitair Medisch Centrum. Onder leiding van mw. dr. C.F. Allaart en prof. dr. T.W.J. Huizinga werkte zij aan het onderzoek beschreven in dit proefschrift.

Sinds januari 2014 is zij werkzaam als arts-assistent Interne Geneeskunde in het Rijnland ziekenhuis te Leiderdorp. In mei 2014 is zij gestart met de opleiding Interne Geneeskunde aan het Leids Universitair Medisch Centrum (opleider: prof. dr. J.W. de Fijter), het eerste deel van de opleiding tot internist zal ze volgen in het Rijnland ziekenhuis te Leiderdorp (opleider: drs. S. Anten).

DANKWOORD

Op deze plaats wil ik iedereen bedanken die heeft bijgedragen aan het tot stand komen van dit proefschrift.

Allereerst mijn promotor en co-promotor. Prof. dr. T.W.J. Huizinga, beste Tom, bedankt voor het enthousiasme waarmee je de afgelopen jaren meedacht en de verfrissende kijk op mijn manuscripten, voor je luisterend oor en het feit dat je altijd benieuwd bent hoe het met me gaat. Dr. C.F. Allaart, beste Renée, bedankt voor alles wat ik van je heb geleerd, van het managen van een multicenter onderzoek tot het schrijven van stukken. Je enthousiasme, goede adviezen en bemoedigende woorden zijn van grote waarde geweest tijdens het schrijven van dit proefschrift.

Mijn dank gaat uit naar alle reumatologen, reumatologen in opleiding en alle onderzoeksverpleegkundigen en reumaconsulenten in het LUMC en in de perifere ziekenhuizen, voor het includeren en jarenlang volgen van patiënten. Natuurlijk veel dank aan alle patiënten die meededen aan de onderzoeken, zonder uw medewerking en tijd was dit allemaal niet mogelijk.

Het secretariaat van het stafcentrum reumatologie: Joyce, Hanny, Hughine en Nancy, dank voor jullie ondersteuning, advies en interesse in mij. Het datamanagement, Jozé en Cedric, veel dank voor jullie ondersteuning en de snelle hulp met allerhande pop-ups, errors en andere computerdrama's.

Dr. E.J. Giltay, beste Erik en prof. dr. R.C. van der Mast, beste Roos, veel dank voor alle hulp en de zorgvuldige kanttekeningen tijdens het schrijven van het manuscript over optimisme en depressieve symptomen bij patiënten met artritis. Prof. dr. W.F. Lems en dr. P.J.S.M. Kerstens, dank voor het meelezen en alle toevoegingen aan het BeSt manuscript in dit proefschrift. Dr. S. Le Cessie, beste Saskia en dr. B. Siegerink, beste Bob, bedankt voor jullie hulp en waardevolle statistische inzichten.

Veel dank aan alle promovendi waarmee ik de afgelopen jaren heb samengewerkt, voor zowel de gezelligheid, als de (meestal) zinvolle discussies: Rachel, Annemiek, Jessica van Nies, Diederik, Annemarie, Hanna, Manouk, Jessica Meijs, Emilia, Wing-Yee, Angga, Emalie, Rani, Rosanne, Els, Wouter, Lukas, Wendy en Pauline.

Een aantal mensen wil ik in het bijzonder bedanken:

Kirsten, door jou raakte ik wegwijs op de afdeling en in de IMPROVED-studie. Veel dank voor de fijne samenwerking tijdens het schrijven van manuscripten en het draaiende houden van de IMPROVED-studie.

Gülsah, het 'IMPROVED-stokje' is nu aan jou overgedragen. Bedankt voor de samenwerking tijdens het laatste jaar van mijn promotietijd.

Linda, dank voor al je wijze raad, statistische adviezen, het meelezen en natuurlijk de BBB's. Super dat je mijn paranimf wilt zijn!

Marianne, bedankt voor de hulp en adviezen de afgelopen jaren. Zowel de samenwerking tijdens het schrijven van het BMI-stuk, als het monitoren in Brabant en Zeeland (via Antwerpen) zal ik niet snel vergeten!

Willemien, mijn 'eiland-genoot' tijdens mijn gehele promotietijd, dank dat je altijd even mee wilde denken of lezen.

Iris, dank voor je humor en stralende humeur en de prettige samenwerking.

Jill, bedankt voor de samenwerking tijdens het scoren en het schrijven van het PROMPT-stuk en voor de vele goede gesprekken.

Badelog en Rosaline, jullie beiden wil ik bedanken voor de steun en aanmoediging op de afdeling en jullie vriendschap daarbuiten.

Al mijn lieve vrienden, dat ik jullie niet allemaal bij naam noem doet niets af aan wat jullie voor me betekenen. Ik ben jullie dankbaar voor jullie belangstelling, jullie steun en alle gezelligheid!

Lieve Miek, de afgelopen jaren heb je vaak naar me geluisterd en me van advies voorzien en daar ben ik je enorm dankbaar voor. Ik hoop dat ik ook de komende jaren op je mag blijven leunen.

Lieve Hes, dank voor al je adviezen en je bemoedigende woorden en het meejuichen als ik weer een stapje verder was gekomen in mijn onderzoek. Ik ben blij dat je mijn grote zus bent, fantastisch dat je mijn paranimf wilt zijn!

Lieve papa, heel veel dank voor het vertrouwen en de mogelijkheden die jij en mama me gegeven hebben. Dat mama dit niet heeft mogen meemaken is een groot gemis.
Ik dank jou en Yvonne voor jullie steun en verregaande interesse tijdens de afgelopen jaren.

En ten slotte natuurlijk Jeroen, mijn allerliefste. Mijn dank aan jou is buitengewoon groot; voor je interesse in de dingen die ik doe, je luisterend oor in tijden van klagen, je relativeringsvermogen en humor als je met me meedenkt en bovenal voor je liefde. Samen met jou kan ik alles aan, ik kijk enorm uit naar onze toekomst!