Improving targeted treatment in early rheumatoid and undifferentiated arthritis

Akdemir, G.

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Gülşah Akdemir

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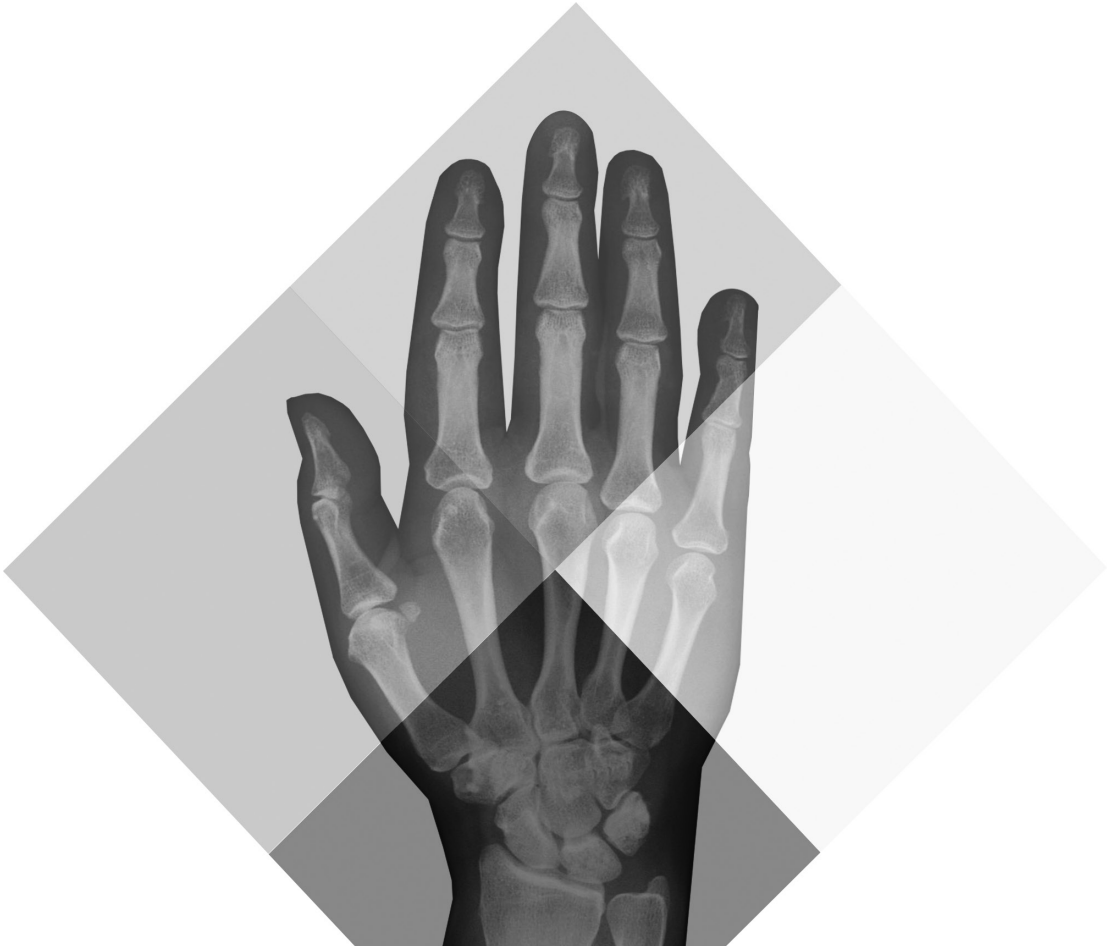
CONTENTS

Chapter 1

GENERAL INTRODUCTION



RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a systemic autoimmune disorder of unknown aetiology, characterized by chronic inflammation of synovial tissue in peripheral joints.[1] Genetic and environmental factors - for instance smoking - may partly cause the disease, which affects around 0.5-1% of the population.[1] The arthritis is typically symmetrical and generally affects the small joints in the hands and feet, however other joints of the upper and lower limb are also commonly affected. Patients present with symptoms of pain, (morning) stiffness and swelling of joints. Untreated, the disease can lead to destruction of joints due to erosions of cartilage and bone, causing joint deformities due to stretching of tendons and ligaments.[1,2] Joint destruction can lead to physical function loss, incapability to carry out daily tasks of living (e.g. opening jars, dressing, brushing hair, getting up from a chair, walking) and difficulties in maintaining employment. Also, systemic effects such as interstitial lung disease or cardiovascular disease can occur due to vasculitis.[1] Approximately one-third of patients suffer in the acute phase of polyarthritis from low-grade fever, weight loss, myalgia, fatigue, and depression.

Classification criteria for RA were developed in 1987[3] and renewed in 2010[4] (figure 1). The new criteria were developed to identify RA patients in an earlier stage of the disease course. Previous studies have shown that patients benefit from early treatment after onset of symptoms. Therefore it is important to diagnose RA patients in an early stage. In addition, anti-citrullinated protein antibodies (ACPA) were added to the new criteria, as early RA patients will more often present with ACPA compared to patients with another arthritic disease.

ACR 1987 criteria A score ≥4/7 must be present Criteria 1-4 must have been present for at least 6 weeks.	**ACR/EULAR 2010 criteria** Target population who 1. Has at least 1 joint with definitive clinical synovitis 2. With the synovitis not better explained by another disease A score ≥6/10 needed for classification	
1. Morning stiffness (at least 1 hour)	1. Joint involvement	
2. Arthritis of 3 or more joint areas	1 large joint	0
3. Arthritis of hand joints (≥1 swollen joints)	2-10 large joints	1
4. Symmetrical arthritis	1-3 small joints	2
5. Rheumatoid nodules	4-10 small joints	3
6. Serum rheumatoid factor	>10 joints (at least 1 small joint)	5
7. Radiographic changes (erosions)	2. Serology	
	Negative RF and negative ACPA	0
	Low positive RF or low positive ACPA	2
	High positive RF or high positive ACPA	3
	3. Acute phase reactants	
	Normal CRP and normal ESR	0
	Increased CRF or increased ESR	1
	4. Symptom duration	
	<6 weeks	0
	≥6 weeks	1

Figure 1 ACR rheumatoid arthritis classification criteria 1987 and ACR/EULAR 2010 criteria.

AUTOANTIBODIES

Rheumatoid factor (RF) is the classic autoantibody known in RA. Anti-citrullinated protein antibodies (ACPA)[5] were discovered later and play an important role in the classification of RA since 2010. ACPA have a higher specificity than RF and can be detected years before arthritis symptoms occur.[6] In patients with early arthralgia or undifferentiated arthritis, presence of ACPA is associated with progression to RA. In patients with RA, the presence of ACPA is associated with more severe disease outcomes such as radiological joint damage and functional disability[7-14] It is hypothesized that ACPA-negative RA is another disease entity than ACPA-positive RA[15-17] and requires a different treatment approach.[18] However, it is not clear what the optimal treatment for ACPA-negative patients is. Because there is less need to suppress potential future damage, it has been suggested that ACPA-negative RA patients do not require combination therapy with corticosteroids.[18] On the other hand it appears that ACPA-negative patients have a better early clinical response better to anti-tumour necrosis factor alpha (anti-TNFα) agents than ACPA-positive patients.[19-21]

More recently anti-carbamylated protein antibodies (anti-CarP) have been identified. Anti-CarP are associated with severe disease such as radiological progression, even if ACPA

are negative.[13] Like RF and ACPA, anti-CarP can be present before clinical symptoms are noticed.[22-24] It can predict the progression to RA in arthralgia patients, regardless of ACPA status.[14]

UNDIFFERENTIATED ARTHRITIS

Patients who present with arthritis that cannot be identified as (manifestation of) a specific rheumatologic disease, and/or do not fulfil the classification criteria of such a disease, are said to have undifferentiated arthritis (UA). These patients may eventually develop RA (17-32% of patients) or another chronic inflammatory disease or achieve spontaneous remission (40-55% of patients) (percentages depending on the inclusion criteria of various UA cohorts).[25,26] It has been hypothesized that treating patients with antirheumatic drugs may induce remission or at least prevent progression to RA with joint damage. Several therapies have been tried without success.[27-35] The PROMPT study showed that treatment with methotrexate resulted in a delay but not prevention of progression to RA.[32] It may be that once arthritis is clinically manifest, the disease process has already become chronic and difficult to redress. Newer studies have tried to treat UA patients with more effective medications, or in an earlier (subclinical) phase of the disease.

TREATMENT OF RA

Treatment of RA patients has changed considerably in the past decades. Where formerly patients were treated with disease modifying antirheumatic drugs (DMARDs) only when damage progression became apparent, this changed to introducing DMARDs as soon as patients were diagnosed with RA.[36-38] Thanks to shorter referral times and in parallel with the new classification criteria, patients are even recognized in earlier phases of the disease process and are treated earlier with antirheumatic therapy. This treatment results in earlier suppression of disease activity and better outcomes.[35,39-43] In addition, tools have been developed and introduced in practice, to measure disease activity and set a target for therapeutic decisions. Although, and because, the choice of drug(s) remains a case of trial and error, it is recommended to measure disease activity (for instance with the Disease Activity Score (DAS), see below) frequently (so called ‘tight control’ policy) and intensify or change the medication until the predefined target is achieved (‘treat to target’ policy). The recommended target is remission[44] or at least low disease activity (and various definitions can be used).[45-47] If patients maintain a disease activity below the treatment target medication can be tapered and stopped, to achieve drug-free remission (DFR).[48]

ANTIRHEUMATIC DRUGS

Antirheumatic treatment can be divided in conventional synthetic (cs)DMARDs, glucocorticosteroids and biological (b)DMARDs.
Current recommendations are to start with a (combination of) csDMARD when the patient is diagnosed with RA. Methotrexate is considered the anchor drug in RA treatment.[49] Although the working mechanisms of methotrexate on inflammation is not exactly known some mechanisms have been proposed. Including the promotion of adenosine release, suppression of inflammation by the inhibition of the production of pro-inflammatory cytokines,[50] inhibition of the novo purine synthesis,[51,52] antiproliferative and apoptosis related mechanisms,[51] an indirect inhibition or cyclo-oxygenases and lipoxygenase products,[51] a reduction of the production of proinflammatory cytokines (interleukin-1 (IL-1), IL-6 and TNFα) and an increase of the gene-expression of anti-inflammatory cytokines (IL-4 and IL-10).[51] As an alternative sulfasalazine or leflunomide can replace methotrexate in case of contraindications (chronic liver disease, excessive alcohol use, leucopenia, thrombocytopenia, acute or chronic infections or severe renal impairment) or intolerance.[53] Corticosteroids are often combined with a csDMARD. Early treatment in the disease course with short-term high dose prednisone has proved to be effective in reducing inflammation and prevention of joint damage.[48] The long term adverse events like cardiovascular risk, infections, osteoporosis and diabetes mellitus form a concern in treating patients with corticosteroids. However, in daily practice low dosages are prescribed and then these concerns may not be relevant.[54] Clinical trials have shown that initial treatment with a combination of csDMARDs followed by a treat-to-target approach is effective in RA patients.[32,35,39-43] Patients that have arthritis affecting one joint can be treated by an intra-articular injection with prednisone.[55] Relapse chance of the arthritis is high and a reinjection cannot be given limitless in the same joint.[55] As an alternative intra-articular injection with a bDMARD was tried, however this is not superior over prednisone.[56-60] In patients that fail after initial csDMARD therapy and another csDMARD a bDMARD is recommended.[49] BDMARDs are genetically-engineered proteins derived from human genes and are effective in the inflammatory cascade where pro-inflammatory cytokines are blocked or lymphocytes are inhibited or depleted. A combination with a csDMARD is preferable. The first bDMARD was introduced in 1990, a TNFα-blocker. In head to head comparison trials bDMARDs give an earlier response and are more effective than MTX monotherapy.[61,62] However, the high costs and higher risks of infectious side effects result in that most patients do not start with a bDMARD as initial treatment. There are conditions to be fulfilled for reimbursement of bDMARDs. Recommendations follow this practice.[63]

DISEASE OUTCOMES

Disease activity score

The disease activity score (DAS) is a composite outcome measure consisting of the Ritchie articular index (RAI)[64] a 53 tender joint count, the swollen joint count (SJC) (out of 44 joints), general health as indicated by the patient on a visual analogue scale (VAS) (0-100 mm), and the erythrocyte sedimentation rate (ESR). This score has been validated in several studies and can be calculated according to the following formula: $DAS=0.54\sqrt{RAI}+ 0.065*SJC + 0.33*\ln ESR + 0.0072*GH$.

High disease activity is defined by a DAS>2.4, low disease activity by a DAS≥1.6 - ≤2.4 and remission by a DAS<1.6. It is suggested to target treatment at DAS-remission.[63] Even a stricter definition was defined by the ACR/EULAR task force in 2011[46]: TJC, SJC (out of 28 joints, feet among other joints excluded), C-reactive protein and general health as indicated by the patient on a VAS all ≤1.

Functional ability

Functional ability can be measured by the health assessment questionnaire (HAQ).[65] The HAQ is a self-administered questionnaire that measures the level of difficulties patients experience with activities of daily living and the level of assistance that is required in these activities. There are 8 categories with 3 questions about dressing, rising, eating, walking, hygiene, reach, grip and activities like errands and chores. Every question can be graded from 0 (no disability) to 3 (unable to do). The sum of the highest score of the 8 categories divided by 8 the HAQ disability score can be calculated ranging from 0 to 3. A value above 1 represents functional disability.[66,67] Improvement of 0.22 is considered as the minimum clinically important difference.[68]

Health related quality of life

Health related quality of life (HRQoL) can be measured by the Short Form (SF)-36,[69] a validated generic, general health status questionnaire that focuses on non-physical aspects of chronic disease like anxiety and depression and social functioning. The questionnaire contains eight domains which consist of: physical functioning, role limitations due to physical and due to emotional functioning, bodily pain, general health, vitality, social functioning and mental health. The score per domain can range from 0 (worst) to 100 (best). Two summary component scores can be calculated by these 8 domains: a physical component score (PCS) and a mental component score (MCS). These scores are standardized to the population norm of mean 50 and standard deviation 10. The minimum clinical important difference is 2.5-5 points for the component scores.[70]

Joint damage

Radiographs of hands and feet can be made to monitor joint damage in RA patients. In clinical trials the radiographs are evaluated in 44 joints for erosions (0-5) and joint space narrowing (0-4) by the modified Sharp/van der Heijde score (SHS)[71] ranging from 0 to 448. Joint damage progression can be calculated by increase in damage compared to baseline. The minimal clinically important difference for progression is 5 points.[72] Rapid radiological progression (RRP) is defined by a deterioration of 5 points in the first year of treatment.

Bone mineral density measurements

An early manifestation of RA is a loss of metacarpal bone mineral density (mBMD) which can be measured by Digital X ray Radiogrammetry (DXR). Persistent disease activity is associated with mBMD loss and patients in prolonged clinical remission show mBMD gain.[73-76] mBMD loss in the first months of treatment is predictive for joint damage progression after 1 year.[77]

THE IMPROVED-STUDY

The Induction therapy with Methotrexate and Prednisone in Rheumatoid Or Very Early arthritic Disease (IMPROVED)-study is a multicentre two-step randomized single-blinded clinical trial in 610 RA and UA patients included between March 2007 and September 2010. The study was designed by Dutch rheumatologists participating in the Foundation for Applied Rheumatology Research (FARR). The study was conducted in 12 hospitals in the Western part of the Netherlands.

It has become clear that monitoring disease activity and adjusting the medication until a predefined level of suppression is achieved ('treatment to target') prevents gradual deterioration.[41,78] In the BeSt-study, with treatment strategies targeting at low disease activity, many patients even achieved clinical remission.[48] Remission may now be the optimal target, particularly in early arthritis patients. However, in the PROMPT study, methotrexate monotherapy proved insufficient to permanently induce remission in patients with undifferentiated arthritis.[32] In the BeSt-study, in classifiable RA patients, a combination of antirheumatic drugs including a tapered high dose of prednisone resulted in earlier clinical improvement and less damage progression than methotrexate monotherapy.[41,48] Medication could often be tapered and even discontinued, so that some patients achieved DFR.

The IMPROVED-study builds on the intension and results of these studies. It includes both patients with early RA (based on the new classification criteria) and patients with undifferentiated arthritis (UA) of ≥18 years, a DAS ≥1.6 and no previous antirheumatic therapy. RA was defined as fulfilling the 2010 ACR/EULAR classification criteria[4] 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. The treatment target was DAS-remission (DAS<1.6). All patients started with combination therapy including methotrexate (MTX) 25 mg/week and prednisone 60mg/day tapered in 7 weeks to 7.5mg/day. Patients in early DAS-remission (DAS<1.6 after 4 months) tapered prednisone to 0. When still in remission after eight months, MTX was also tapered to 0. In case of a DAS≥1.6 after 8 months, prednisone was restarted at 7.5mg/day. Patients with a DAS≥1.6 after 4 months were randomized into 2 treatment arms: MTX 25mg/week, hycroxychloroquine (HCQ) 400mg/day, sulfasalazine (SSZ) 2000mg/day and prednisone 7.5mg/day (arm 1), or to MTX 25mg/week plus adalimumab 40mg/2 weeks (arm 2). In arm 1, if DAS-remission was achieved after 8 months, prednisone SSZ and then HCQ were tapered to MTX monotherapy. MTX was stopped if remission remained 4 months later. If remission was not achieved at 8 months, patients switched to MTX+adalimumab. In arm 2 patients tapered adalimumab in case of remission after 8 months, and increased adalimumab to 40mg/week in case of no remission. In both arms if patients did not achieve remission on a combination of MTX+adalimumab 40mg/week, further treatment decisions were left to the opinion of the rheumatologist. Patients and rheumatologists were not blind for treatment allocation. Only the trained research nurses were blind to allocation and provided an objective assessment of the DAS at every 4 months. The study includes drug tapering and discontinuation strategies, not after prolonged low disease activity as in the BeSt-study, but as soon and as long as remission is achieved, aiming to avoid prolonged exposure to prednisone and other medications and achieve early DFR.

Primary outcomes were percentages of patients in DAS-remission and DFR based on a DAS<1.6,[44] or on the proposed remission definition published by the ACR/EULAR in 2011 (Boolean).[46] Secondary outcomes were mean DAS, mean functional ability measured by the Dutch version of the Health Assessment Questionnaire (HAQ), radiological damage progression of the joints in hands and feet measured by the Sharp-van der Heijde score (SHS) and toxicity. Baseline and annual radiographs of hands and feet were scored by 2 readers blinded for patient identity and allocation either in time random order or in chronological order for presence of erosions and joint space narrowing.

The first results of the IMPROVED-study showed that it is possible for 61% of the RA patients and 65% of the UA patients to achieve early remission (DAS<1.6) after 4 months treatment with MTX and a tapered high dose of prednisone. Radiological joint damage progression was almost completely suppressed.

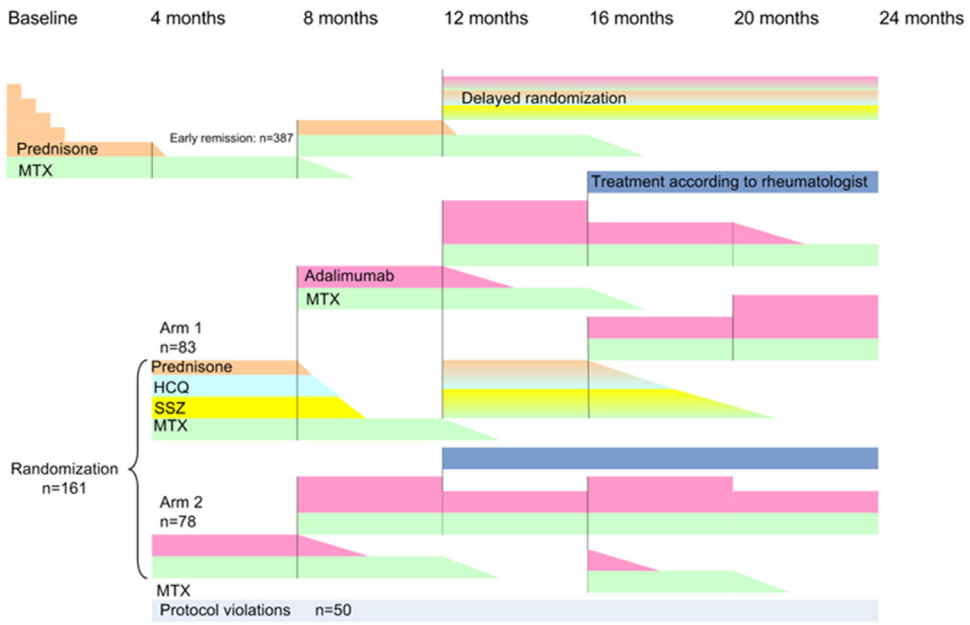


Figure 2 Flow chart IMPROVED study
MTX: methotrexate, 25mg/week; HCQ: hydroxychloroquine; SSZ: sulphasalazine. Colours: orange=prednisone, green=MTX, dark blue=treatment according to opinion rheumatologist (TAR), aqua=HCQ, yellow=SSZ, purple=adalimumab biweekly, double thickness purple=adalimumab weekly, grey=protocol not followed as required but remained in follow-up (outside of protocol, OOP).
All patients started with MTX and prednisone, tapered from 60mg/day to 7.5mg/day in 7 weeks. After 4 months if patients were in remission (DAS<1.6) prednisone was tapered to MTX monotherapy. If patients were not in remission they were randomized to arm 1 (MTX 25mg/week, HCQ 400mg/day, SSZ 2000mg/day and prednisone 7.5mg/day) or arm 2 (MTX 25mg/week plus adalimumab 40mg/2 weeks). Every four months if patients were in remission, the medication was tapered or stopped and if patients were not in remission, the medication was intensified or restarted.

OUTLINE OF THIS THESIS

In this thesis we focus on early treatment of early RA patients and/or patients that do not fulfil the ACR/EULAR 2010 classification criteria (undifferentiated arthritis). Disease outcomes after prolonged treatment to target are described. In addition, conditions or options for further improvements in arthritis treatment were explored. In **chapter 2** the clinical and radiological outcomes after two years of the IMPROVED-study are presented. By induction therapy followed by remission steered treatment we found that joint damage was suppressed in many patients. Only a small group of patients showed radiological progression and we tried to find predictive factors for progression after 2 years, described in **chapter 3**. The clinical and radiological outcomes after 5 years of the IMPROVED-study were explained in **chapter**

4. In **chapter 5** we focussed on outcomes on MRIs in relation to clinical outcomes of patients that were treated by intra-articular injections with methylprednisolone or infliximab for chronic or recurrent gonarthritis with different diagnosis. As ACPA-negative RA might be a different disease entity compared to ACPA-negative RA and therefore might be treated in a different way, we looked in **chapter 6** in the BeSt-study which treatment strategy is more effective in ACPA-negative patients. **Chapter 7** focusses on possible explanations of progression of joint space narrowing, in particular in relation to different age groups in the BeSt study. In **chapter 8** we looked which treatment target is more beneficial for RA patients; low disease activity (DAS≤2.4 BeSt-study) or DAS-remission (DAS<1.6 IMPROVED-study). In relation to that, in **chapter 9** we focussed on whether rheumatologists' adherence to these treatment protocols might be dependent on the target.

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Chapter 2

TWO-YEAR RESULTS OF DAS-REMISSION STEERED TREATMENT STRATEGIES AIMING AT DRUG FREE REMISSION IN EARLY ARTHRITIS PATIENTS (THE IMPROVED-STUDY)

Gülşah Akdemir*, Lotte Heimans*, Kirsten V.C. Wevers-de Boer, Yvonne P. Goekoop-Ruiterman, Esmeralda T. Molenaar, Hans H.L.M. van Groenendael, André J. Peeters, Gerda M. Steup-Beekman, Leroy R. Lard, Peter B.J. de Sonnaville, Bernard A.M. Grillet, Tom W.J. Huizinga, Cornelia F. Allaart.
* both authors contributed equally

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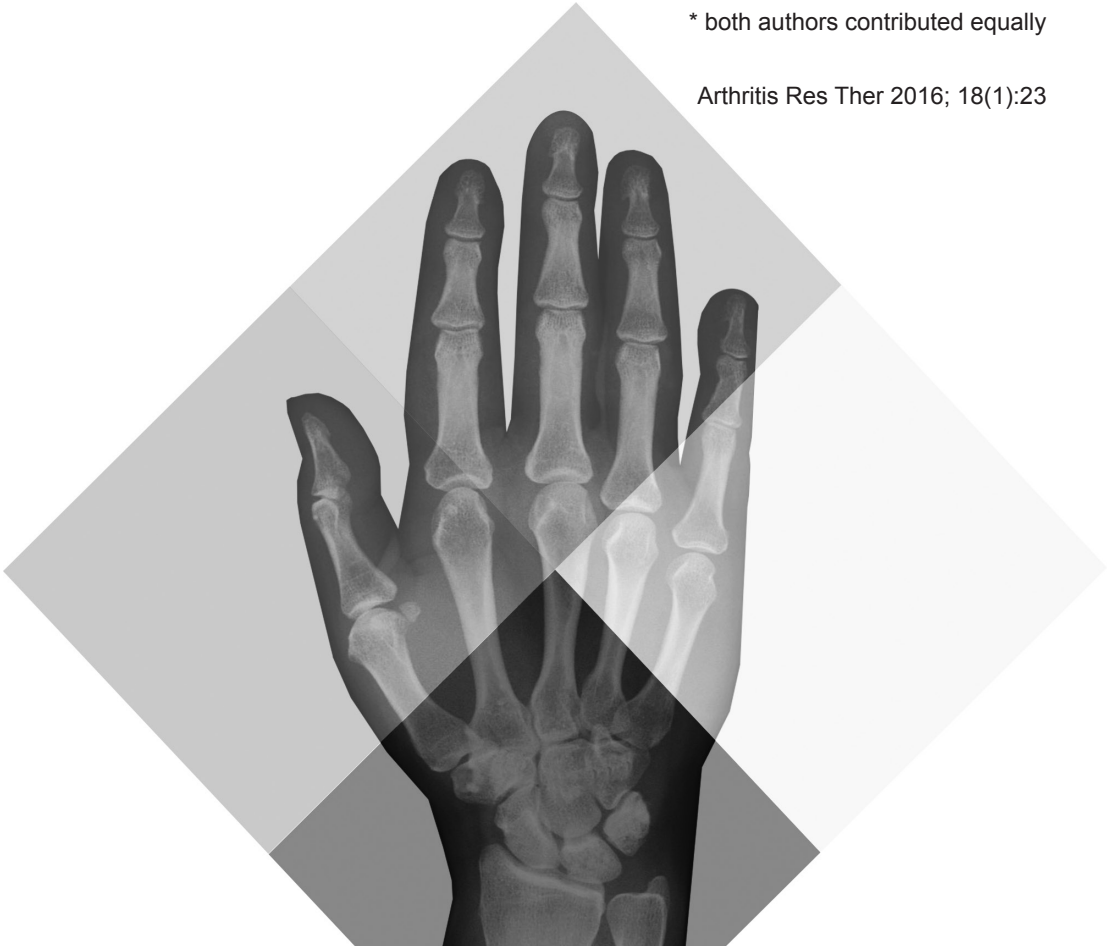

ABSTRACT

Introduction

Early suppression of disease activity in (rheumatoid) arthritis (RA) patients may result in drug free remission and prevent damage. We assessed 2-year clinical and radiological outcomes of two DAS-remission steered treatment strategies in early arthritis patients.

Methods

610 patients with early RA or undifferentiated arthritis (UA) were treated with methotrexate (MTX) and tapered high dose of prednisone. Patients in early remission (44/53 joints disease activity score (DAS) <1.6) after 4 months tapered and stopped medication. Patients who did not achieve early DAS-remission were randomized to either MTX plus hydroxychloroquine plus sulphasalazine plus low dose prednisone (arm 1) or to MTX+adalimumab (arm 2). At four-monthly intervals, medication was tapered and stopped if DAS<1.6 but restarted, increased or switched if DAS≥1.6. Proportions of (drug free) DAS-remission (DFR) after 2 years and Sharp-van der Heijde scores (SHS) were analyzed separately for the treatment strategies and patients with RA and UA.

Results

After 2 years, 301/610 (49%) patients were in DAS-remission and 131/610 (21%) in DFR. In the early remission group 241/387 patients (62%) were in DAS-remission and 111/387 (29%) DFR. In arm 1 22/83 (27%) and in arm 2 24/78 (31%) were in DAS-remission, and 6/83 (7%) and 7/78 (9%), respectively, were in DFR. RA and UA patients achieved DAS-remission in comparable percentages (RA: 234/479 (49%), UA: 64/122 (52%), p=0.25). More UA patients achieved DFR (41/122 (34%)) compared to RA patients (89/479 (19%), p<0.001). Mean (SD) DAS over time was 1.74 (0.58) across all patients, and median (IQR) SHS progression was 0 (0-0).

Conclusions

After 2 years remission steered treatment in early RA and UA patients, DAS-remission and DFR percentages were relatively low. Patients who achieved early remission more often achieved (drug free) remission after 2 years than patients who needed additional treatment steps in the randomization arms, and more UA than RA patients achieved DFR. Overall, disease activity and radiologic damage progression in all patients were well suppressed.

INTRODUCTION

In the last decades the treatment of rheumatoid arthritis (RA) has considerably changed, aiming at earlier suppression of disease activity and resulting in better outcomes.[1-3] The need to start disease modifying antirheumatic drugs (DMARD) earlier is incorporated through new classification criteria for RA,[4] which include patients in earlier phases of the disease process. In addition, several trials have included or focused on patients with arthritis not (yet) fulfilling these criteria (undifferentiated arthritis (UA)).[5-13] It has become clear that treatment to target prevents gradual deterioration.[14,15] Based on results of clinical trials with a treatment to target where a large percentage of RA patients achieved clinical remission,[16-18] it is suggested that remission should be the treatment target.[15] Several trials [5,16-20] have shown that initial treatment with a combination including methotrexate (MTX) and corticosteroids result in earlier suppression of inflammation and damage progression. It is hypothesized that early remission induction may prevent chronicity of arthritis and allow tapering of treatment to drug free remission (DFR).[21] In UA this may be even more readily achieved, although in the PROMPT study, monotherapy with MTX proved insufficient to permanently induce remission in patients with UA.[10]

The IMPROVED-study was designed following the intention and results of these studies. It aims to achieve early clinical remission, followed by tapering of medication to DFR. Both patients with early RA (based on the new classification criteria) and patients with UA were included, and treated according to the same protocol, starting with a combination of MTX with prednisone, then tapering or adding DMARD depending on whether the treatment target clinical remission has been achieved. In this secondary analysis of the IMPROVED-study, the clinical and radiological outcomes of two years of remission targeted treatment are presented.

METHODS

Study design

The IMPROVED-study (ISRCTN11916566 and EudraCT number 2006-06186-16) is a multicentre two-step 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 centre (listed in the acknowledgements section).

Patients

Patients were ≥18 years, with early RA or UA, a disease activity score (DAS)≥1.6, and no previous antirheumatic therapy. RA was defined as fulfilling the 2010 American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) classification criteria [4] 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 previously published.[13,22] All patients gave written informed consent.

Intervention

All patients started with four months of MTX 25 mg/week and prednisone 60 mg/day tapered to 7.5 mg/day in 7 weeks. Every four months the DAS (based on a44 swollen joint count and the Richie articular index, both including the feet)[23] 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).[24]

Patients in early remission (DAS<1.6 after four months) tapered prednisone in three weeks with a dose reduction of 2.5 mg/day each week to 0. When still in remission after eight months, MTX was also tapered to 0 in ten weeks (every week tapered with 2.5mg/wk). In case of a DAS≥1.6 after eight months, prednisone was restarted at 7.5 mg/day.

Patients with a DAS≥1.6 after four 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 to arm 1 or 2 (‘delayed randomization’) (figure 1). In arm 1, if remission after eight months was achieved, prednisone, SSZ and then HCQ were stopped. MTX was stopped if remission remained four months later. If remission was not achieved at eight 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 eight months, and increased ADA to 40mg/week in case of no remission. The weekly dose of adalimumab (in combination with MTX) was exploratory and is not evidence based. Based on the costs of medication, and in view of a subsequent report on dose dependent risks for side effects, in current daily practice adalimumab 40 mg/week is not approved.[25]

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 previously published.[22]

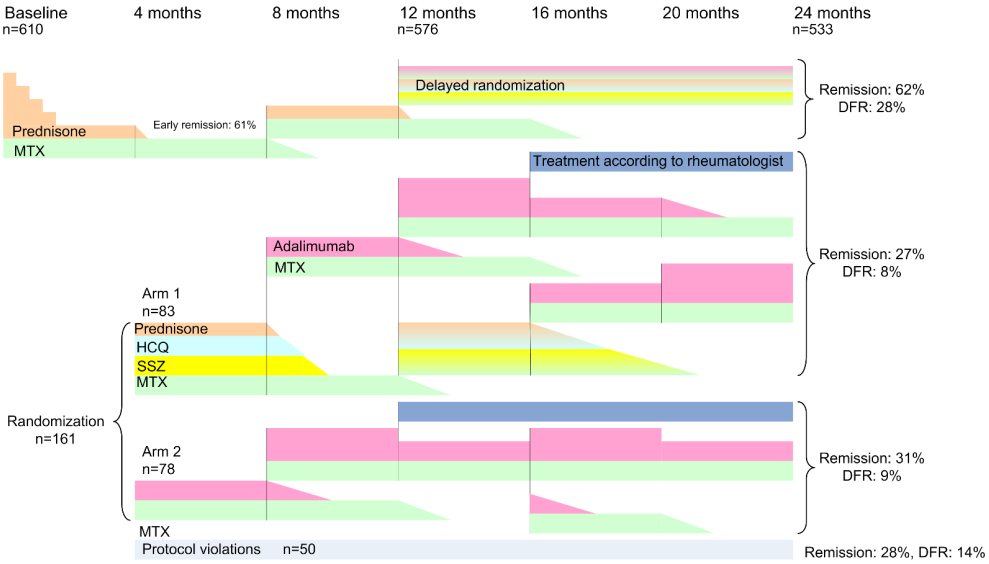

Figure 1. Study flow chart with percentages DAS- and drug free remission after the second study year.
DFR: drug free remission, MTX: methotrexate, HCQ: hydroxychloroquine, SSZ: sulfasalazine. Colours: orange=prednisone, green=MTX, dark blue=treatment according to opinion rheumatologist (TAR), aqua=HCQ,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

Primary and secondary outcomes

Primary outcomes were percentages of patients in DAS-remission and DFR based on a DAS<1.6.

Secondary outcomes were DFR based on the proposed remission definition published by the ACR/EULAR in 2011 (Boolean)[26] mean DAS, mean functional ability as measured by the Dutch version of the Health Assessment Questionnaire (HAQ),[27] 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))[28] and toxicity.

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 two 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.[29] In 443 of 496 patients who had radiographs taken after two 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 RA and UA patients, and between patients in or not in remission after two years.

Treatment during two years was plotted in a figure as percentages of patients on medication per treatment group. The figure shows not treatment steps but actual medication use, with categorized as 'other' all medications that were prescribed either according to the protocol after failure on adalimumab ('treatment according to physician') or outside the regular treatment steps although still DAS-remission steered ('outside of protocol').

Statistical analysis

We performed intention-to-treat analyses. Outcomes were compared using students *t*-tests, Mann Whitney U tests and χ^2- tests. DAS and HAQ over time were compared using linear mixed models (LMM), 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.

RESULTS

Study population

Of the 610 patients, 479 (79%) had classifiable RA (2010 criteria) and 122 (20%) UA (nine patients could not be classified because of missing data). Of 610 patients, 387 (63%) achieved early DAS-remission at four months (Early remission group). One-hundred-sixty-one of 610 patients (26%) with DAS≥1.6 at four months were randomized; 83 patients to arm 1 and 78 to arm 2. Fifty patients with a DAS≥1.6 at four months were not randomized because the treating physician declared the patient in clinical remission. These patients were analysed in the outside of protocol (OOP)-group. Twelve patients left the study before the assessment at four months (table 1). Over two years 79 patients were lost to follow-up; 54 withdrew consent, nine discontinued because of a revised diagnosis, and eight because of co-morbidity. Eight patients died,[13,22] three of those in the second year of the study (additional file 1).

Table 1. Baseline characteristics of the IMPROVED-study population.

	Total	Early remission	Arm 1	Arm 2	OOP
	n=610	n = 387	n = 83	n = 78	n = 50
DAS, mean ± SD	3.2 ± 0.9	3.0 ± 0.8	3.6 ± 0.9	3.6 ±1.0	3.6 ±0.9
HAQ, mean ± SD	1.2 ± 0.7	1.0 ± 0.7	1.4 ± 0.6	1.4 ± 0.6	1.3 ± 0.7
Age in years, mean ± SD	52 ± 14	52 ± 14	49 ± 14	51 ± 14	54 ± 14
Female, n (%)	414 (68)	240 (62)	64 (77)	58 (74)	42 (84)
Symptom duration (weeks), median (IQR)	18 (9-32)	17 (9-30)	22 (9-41)	21 (8-31)	18 (9-42)
RF positive, n (%)	339 (56)	224 (58)	41 (49)	43 (55)	23 (46)
ACPA positive, n (%)	333 (55)	225 (58)	40 (48)	37 (47)	25 (50)
RA(2010), n (%)	479 (79)	298 (77)	66 (80)	66 (85)	40 (80)
Swollen Joint Count, median (IQR)	5 (3-10)	5 (2-9)	6 (3-10)	8 (4-12)	7 (3-13)
Tender Joint Count, median (IQR)	6 (4-9)	5 (3-8)	8 (6-13)	9 (6-13)	8 (6-14)
ESR mm/hr, median (IQR)	25 (11-39)	23 (8-38)	28 (13-41)	22 (11-41)	29 (16-42)
VAS global health (mm), mean ± SD	46 ± 23	43 ± 24	53 ± 20	54 ± 22	49 ± 23
Total SHS, median (IQR)	0 (0-1.0)	0 (0-0.5)	0 (0-0)	0 (0-0)	0 (0-0)
Erosive, n (%)	89 (15)	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.
OOP: 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 antibodies, 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.

DAS-remission and drug free remission

Fifty-five of the 610 patients (9%) (37 RA, 17 UA, p=0.01, and one patient unclassifiable because of missing data) were in sustained DAS-remission from four months through to two years and therefore in DFR from eight months to two years. Fifty patients (8%) never achieved DAS-remission during two years follow-up. For patients who achieved DAS-remission but lost it again after drug tapering, medication was reintroduced. At the next evaluation, 75% of those patients were again in DAS-remission. At t=2 years, 301/610 (49%) patients were in DAS-remission and 131/610 (21%) were in DFR. In the early remission group, 241/387 (62%) were in DAS-remission and 111/387 (29%) in DFR at t=2 years. Twenty-two of 83 patients (27%) in arm 1, and 24/78 (31%) in arm 2, were in DAS-remission (p=0.76), and 6/83 patients (7%) in arm 1 and in 7/78 patients (9%) in arm 2 were in DFR at t=2 years (p=0.73). Finally, at t=2 years, 138 of all 610 patients (23%) were in ACR/EULAR remission (Boolean); 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).

At t=2 years, comparable percentages of anti-citrullinated protein antibodies (ACPA)-positive and ACPA-negative patients were in DAS-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 UA or RA patients achieved remission after two years (UA: 64/122 (52%) and RA: 234/479 (49%), p=0.25), but significantly more UA patients, of whom 94% were ACPA-negative, achieved DFR (41/122 (34%) compared to 89/479 (19%) in RA patients, p<0.001) (supplementary table 1).

DAS and HAQ after 2 years

Patients in DAS-remission at 2 years had a mean (SD) HAQ of 0.29 (0.39) compared to 0.94 (0.63) in patients who were not in remission (p<0.001), and a mean (SD) DAS of 0.92 (0.38), compared to 2.32 (0.57) in patients who were not in DAS-remission (p<0.001). This resulted from significant differences in both subjective and (semi-)objective DAS components. Symptom duration at inclusion was not related to achieving or not achieving DAS-remission at t=2 years. Of 204 patients who at baseline had <12 weeks symptom duration, 106 (52%) were in DAS-remission and 50 (25%) were in DFR at 2 years, compared to 192/397 (50%) (p=0.31) and 80/397 (20%) (p=0.19) of those who had had symptoms for ≥12 weeks.

For all patients mean (SD) DAS over time was 1.74 (0.58) and mean HAQ 0.61 (0.47). In the early remission group this was 1.25 (0.77) and 0.38 (0.48), in arm 1, 2.02 (0.70) and 0.9 (0.66), and in arm 2, 1.92 (0.85) and 0.83 (0.67). (table 2 and figure 2). Over time, DAS nor HAQ were 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)) (figure 2).

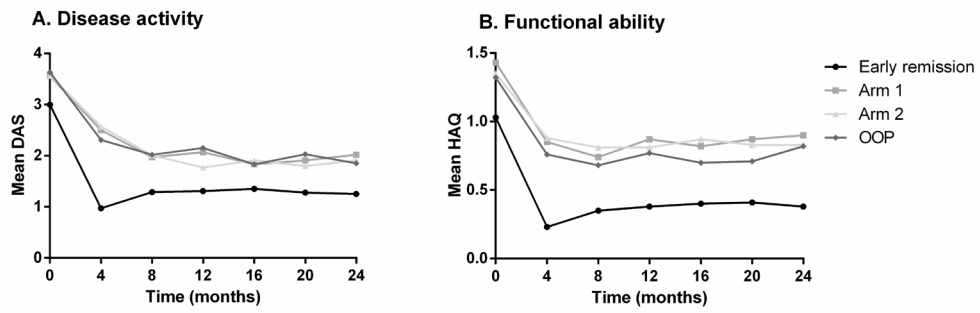

Figure 2: Mean DAS and HAQ according to treatment group during 2 year follow-up.
DAS: disease activity score, HAQ: Health Assessment Questionnaire, OOP: outside of protocol.

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

	Total N=610	Early remission n = 387	Arm 1 n = 83	Arm 2 n = 78	p value arm 1 vs 2	OOP n = 50
DAS, mean ± SD	1.5 ± 0.8	1.3 ± 0.8	2.0 ± 0.7	1.9 ± 0.9	0.45	1.9 ± 0.7
HAQ, mean ± SD	0.5 ± 0.6	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)	0 (0-1)	1 (0-2)	0 (0-2)	0.25	0 (0-2)
Tender Joint Count, median (IQR)	1 (0-3)	0 (0-2)	3 (2-5)	3 (1-6)	0.84	2 (1-4)
ESR mm/hr, median (IQR)	9 (5-17)	8 (4-16)	11 (6-20)	9 (6-17)	0.19	14 (7-25)
VAS global health (mm), mean ± SD	22 ± 22	18 ± 21	30 ± 21	28 ± 24	0.61	32 ± 22
Total SHS, median (IQR)	0 (0-0.5)	0 (0-0.5)	0 (0-1.1)	0 (0-0)	0.12	0 (0-0.3)
Erosive, n (%)	50 (8)	39 (10)	2 (2)	8 (10)	0.04	1 (2)
SHS progression, n (%)	50 (8)	33 (9)	9 (11)	5 (6)	0.31	3 (6)
DAS-remission, n (%)	301 (49)	241 (62)	22 (27)	24 (31)	0.76	14 (28)
Drug free remission, n (%)	131 (22)	111 (29)	6 (7)	7 (9)	0.73	7 (14)
ACR/EULAR remission, n (%)	138 (23)	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.
OOP: 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,[24] 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.[26]
Arm 1: randomized after 4 months to methotrexate, sulphasalazine, hydroxychloroquine and low dose prednisone. Arm 2: randomized after 4 months to methotrexate and adalimumab.

Radiological joint damage

Median SHS progression in all groups was 0 (range 0-22). Only 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 OOP-group 3/50 (6%). There was no significant difference in progression score between patients who at two years were in DAS-remission and patients who were not. Eight of the 610 patients (1%) after two years had radiological damage progression of ≥5 points which represents the minimal clinically important difference.[30] Seven of these eight patients were in early remission after four months and tapered prednisone to zero, whereafter 5 relapsed, needing to restart prednisone. One patient did not achieve early remission and was randomized to arm 2. After 2 years, erosions on radiographs of hands or feet were seen in 39/387 (10%) of patients in the early remission group, in 2/83 (2%) in arm 1, and 8/78 (10%) in arm 2 (arm 1 versus arm 2: p=0.04), and in 1/50 (2%) of patients in the OOP-group.

Therapy

Percentage of patients on various medications according to the prescribed treatment steps per four months in the early remission group, in arm 1, and in arm 2 are depicted in figure 3. In the early remission group treatment with prednisone decreased from 100% of patients at treatment start to less than 10% at t=2 years (figure 3A). Having all started also with MTX treatment, 45% still used MTX at t=2 years. Fifteen percent of patients in the early remission group, after having lost DAS-remission, did not regain DAS-remission after restart of prednisone and were randomized to arm 1 or 2.

In arm 1, over 2 years of treatment 52/83 (63%) patients failed to achieve DAS-remission on the combination of MTX with sulfasalazine, hydroxychloroquine and prednisone and started on adalimumab (with MTX), and up to 39% of these increased adalimumab to once weekly by protocol. Over time, most patients discontinued adalimumab, but due to late switchers and also restarters because of DAS≥1.6, after 2 years 40% of patients in arm 1 were using adalimumab. In arm 2, 40% of patients randomized to treatment with adalimumab initially increasing the dose to 40 mg/week at month 8. The percentage of patients on adalimumab decreased during two years of treatment to 36% (figure 3C), despite. The main difference between arms 1 and 2 thus constitutes the higher initial use of adalimumab in arm 2, while adalimumab use levels out to around 40% of patients at year 2 in both arms. In addition, more patients in arm 2 progressed to other medications. No details are available for the OOP-group, where treatment remained steered at remission, but with medication not as prescribed in the protocol.

Toxicity

Details on toxicity in year 1 were reported previously,[22] showing no significant differences between the treatment arms. 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 OOP-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, five in arm 1, eight in arm 2, and three in the OOP-group (supplementary table 2).

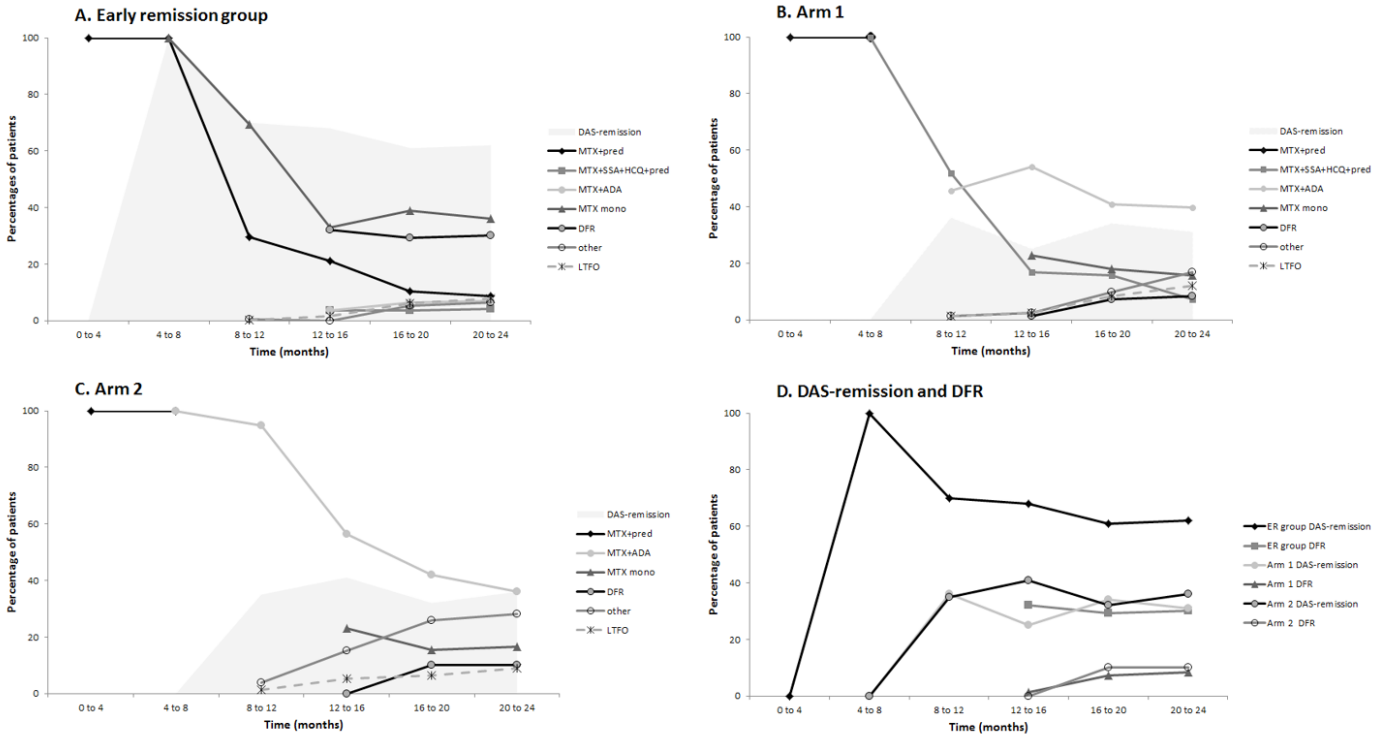

Figure 3: Treatment over time in A. Early remission group, B. Arm 1, C. Arm 2, in percentage of total per treatment group. D. Percentages in DAS-remission and percentages in drug free remission

3A. Early remission group; 3B. Arm 1; 3C. Arm 2. Lines are approximations of the proportions of patients discontinuing medications (according to tapering strategies or due to side effects), or starting medications according to DAS-remission steered escalation strategies, across various treatment steps per arm, over time. The category 'Other' includes medications that were prescribed per protocol in the 'treatment according to rheumatologist' step after failure on methotrexate plus adalimumab, as well as medications prescribed outside of the protocol but still maintaining a DAS-remission targeted strategy. Shaded areas denote patient proportions in DAS-remission over time.

3D. Proportions of patients in DAS-remission and DFR per strategy over time.

Abbreviations: MTX: methotrexate; pred: prednisone; SSA: sulphasalazine; HCQ: hydroxychloroquine; ADA: adalimumab; mono: monotherapy; DFR: drug free (DAS-) remission; LTFO: lost to follow-up; ER: Early remission.

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**	**OOP 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

OOP: outside of protocol, AE: adverse event. *One or more adverse events possible per patient.

DISCUSSION

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

who achieved early DAS-remission after four months more often achieved DAS-remission over time (62% at 2 years) and DFR (29% at 2 years) than patients who did not (29% DAS-remission and 9% DFR at 2 years). There were no differences between the two treatment strategies. Mean DAS over time was significantly lower in the early remission group than in the other groups, but due to DAS-remission steered treatment, mean (SD) DAS over time was low (1.74 (0.58)) across all patients. Radiological damage progression ≥0.5 SHS was seen in only 8% of the patients and functional ability improved, up to the normal range in those who achieved remission and slightly less in the other groups.

The study shows the effectiveness of early DAS-remission steered therapy resulting in low disease activity, improved functional ability and prevention of damage progression. In particular the radiologic results are better than in previous studies such as the remission steered NEO-RACo study where 20-47% of the patients showed progression after two years, and better than in the DAS≤2.4 steered BeSt study, where across the 4 treatment arms 7-33% of the patients showed progression after 1 year.[14,17] This is all the more remarkable as unlike in these studies, we introduced in this study rapid tapering and discontinuation of medication to aim for early drug free remission. The virtual absence of radiographic joint damage progression, which is mainly a pathophysiological important outcome, because minimal damage has little clinical relevance [31] may be related to several trial aspects. We included patients with earlier disease and milder disease activity, less damage at baseline, with fewer patients ACPA-positive, than in the FIN-RACo, NEO-RACo and BeSt study. As in the BeSt and COBRA study, we started treatment with a combination of high dose MTX and a tapered high dose of prednisone, and leaving out sulphasalazine, as in the COBRA-light study [20], which has subsequently shown that a lower dose of prednisone is not less effective than a high dose of prednisone. In addition, we designed the study to be able to introduce a TNF-inhibitor early in the disease course if DAS-remission was not achieved, also for patients with arthritis suspected to have early RA who did not fulfil the classification criteria.

The clinical data are maybe not as spectacular. We had hypothesized that early remission steered treatment including the initial high dose MTX and prednisone and option to expand or switch to multiple csDMARD or adalimumab, would in this study population result in induction of permanent remission in a large number of early arthritis patients. Yet, the overall DAS-remission rates of 49% in the IMPROVED-study are lower than in the NEO-RACo study (60.5%)[17] and only slightly higher than what we observed in the BeSt study (42%).[14,16]

The initial findings were promising. More than 60% of patients achieved DAS-remission after 4 months of treatment, and of those, more than 30% were in drug free remission by the end of year one, and 29% were in drug free remission after 2 years. Those not in early remission were randomized to 2 effective treatment options, with the hypothesis that earlier introduction of anti-TNF might result in more remission and better functional ability. After 1 year we found that patients in arm 2 who were randomized to treatment with adalimumab, achieved more

DAS-remission than patients who were randomized to first try triple-csDMARD-plus-low-dose-prednisone therapy.[22] The weekly dose of adalimumab (in combination with MTX) was exploratory and is not evidence based. In current daily practice this is not approved based on the costs of this medication and the dose dependent risks for infections and malignancies.[25] Fortunately our patients that were treated with this combination of therapy show not significantly more serious infections and malignancies.

After 2 years of DAS-remission steered therapy, this difference was no longer found. Similar results were found in the SWEFOT trial [32] and the RACAT trial.[33] Initial improvement may depend on choice of initial therapy, but late outcomes depend on subsequent targeted treatment. Although delaying adalimumab in arm 1 may have delayed achieving DAS-remission in a proportion of patients, and there are only 2 patients in ACR/EULAR Boolean remission (compared to 14 in arm 2), this has had no relevant impact on radiologic outcomes, nor on the possibility to taper and stop adalimumab (figure 3). This is in contrary to what we previously found in the BeSt study,[16,34,35] where delayed treatment with a TNF-inhibitor was associated with more maintained treatment with that TNF-inhibitor over time.

We were able to taper and stop medication in many patients, effectively avoiding prolonged use of prednisone and (although less so) adalimumab (figure 3) and achieving that 1 in 5 patients were in drug free (DAS-)remission at year 2. However, more patients achieved remission and tapered medication, the majority than had a DAS of >1.6 and had to escalate again. It can be argued that we should not have tapered or tapered and stopped the medication too fast. A longer induction treatment might have suppressed the disease more permanently. Drug free remission in the BeSt study was introduced after up to 2 years of low disease activity and 6 months of DAS-remission. Still 50% of patients who achieved drug free remission had to restart medication because of DAS ≥1.6.[36] Continuous treatment during DAS-remission would have little impact on the radiological outcomes and could induce more side effects. In daily practice, one could consider to taper more slowly, or to a maintenance dose, or substitute methotrexate with hydroxychloroquine before stopping all, but we cannot support that with evidence.

We found that the overall remission rates are relatively low because patients who did not achieve early remission were also less likely to achieve remission later on. It might be that for patients the ‘window of opportunity’ was already missed, even though the outcomes between patients with <12 weeks symptom duration and those with ≥12 weeks symptom duration are comparable. Remission rates and other outcomes except DFR were also comparable between patients with RA and UA. Patients who did not achieve early remission may represent a selected group with more advanced and less responsive disease, who already at baseline have a higher HAQ. Some of these patients may have had non-inflammatory symptoms or non-RA-related ESR that may influence the DAS but will not respond to antirheumatic treatment. For these patients a DAS<1.6 may be unrealistic and remission steered treatment

adjustments may constitute overtreatment. Including and treating patients with UA we risked treating patients with a self-limiting non-RA type of arthritis, who would be among the patients who achieved DFR. At two years, 29% of patients in the early remission group and 7-9% in arms 1 and 2 were in DFR, which is a percentage not too different form the 25% of UA patients who achieved spontaneous remission in the PROMPT trial.[10] We found that UA patients more often achieved DFR than RA patients, and ACPA-negative patients more often than ACPA-positive patients. Interestingly, ACPA positivity was associated with achieving early DAS-remission at four months,[13] and after 1 year of treatment, DAS-remission while on medication was achieved in RA and UA patients, and in ACPA-positive and ACPA-negative patients, in comparable percentages. It appears that RA patients and ACPA-positive patients who achieved DAS-remission will more often flare when medication is tapered and stopped. This may affect future trial designs and daily practice.

CONCLUSION

After 2 years remission steered treatment in early RA and UA patients, DAS-remission and DFR percentages were relatively low. Patients who achieved early remission more often achieved (drug free) remission after 2 years than patients who needed additional treatment steps in the randomization arms, and more UA than RA patients achieved DFR. Radiological damage progression in all patients were well suppressed. As suppression of radiologic damage progression is not enough, additional therapies, medicinal or other, should be investigated to improve clinical outcomes without risk of significant side effects, and further investigations should focus on identifying predictive factors or early markers of effective suppression of disease activity on the initial therapy, to choose the next treatment step and avoid delays in clinical response.

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SUPPLEMENTARY FILE

Table S1. Baseline characteristics and clinical outcomes after 2 years of RA and UA patients.

	RA	UA	
	n=479	**n = 122**	**p-value**
Baseline			
DAS, mean ± SD	3.3 ± 0.9	2.7 ± 0.7	<0.001
HAQ, mean ± SD	1.2 ± 0.7	1.0 ± 0.6	0.02
Age in years, mean ± SD	52 ± 13	52 ± 16	0.90
Female, n (%)	333 (70)	74 (61)	0.06
Symptom duration (weeks), median (IQR)	18 (9-34)	16 (8-28)	0.14
RF positive, n (%)	330 (69)	5 (4)	<0.001
ACPA positive, n (%)	324 (68)	4 (3)	<0.001
Swollen Joint Count, median (IQR)	7 (3-11)	3 (2-6)	<0.001
Tender Joint Count, median (IQR)	7 (4-10)	5 (3-8)	<0.001
ESR mm/hr, median (IQR)	26 (12-41)	16 (9-38)	0.01
VAS global health (mm), mean ± SD	48 ± 24	40 ± 21	0.001
Total SHS, median (IQR)	0 (0-0.5)	0 (0-0.4	0.98
Erosive, n (%)	60 (13)	12 (9)	0.46
2 years			
DAS, mean ± SD	1.5 ± 0.8	1.3 ± 0.8	0.05
HAQ, mean ± SD	0.5 ± 0.6	0.5 ± 0.6	0.88
Swollen Joint Count, median (IQR)	0 (0-1)	0 (0-1)	0.23
Tender Joint Count, median (IQR)	1 (0-3)	1 (0-3)	0.60
ESR mm/hr, median (IQR)	9 (5-19)	7 (3-13)	0.01
VAS global health (mm), mean ± SD	23 ± 23	20 ± 20	0.27
Total SHS, median (IQR)	0 (0-0.5)	0 (0-0.5)	0.88
Erosive, n (%)	42 (9)	7 (6)	0.34
SHS progression, n (%)	41 (9)	9 (7)	0.78
DAS-remission, n (%)	234 (49)	64 (52)	0.25
Drug free remission, n (%)	89 (19)	41 (34)	<0.001
ACR/EULAR remission, n (%)	108 (23)	29 (24)	0.56

Table S2. Serious adverse events during the second year of the IMPROVED-study

	Early remission n=387	**Arm 1 n=83**	**Arm 2 n=78**	**OOP 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).

OOP: outside of protocol, SAE: serious adverse event, PCI: percutaneous coronary intervention.

Chapter 3

PREDICTIVE FACTORS OF RADIOLOGICAL PROGRESSION AFTER TWO YEARS OF REMISSION STEERED TREATMENT IN EARLY ARTHRITIS PATIENTS – A POST-HOC ANALYSIS OF THE IMPROVED STUDY

Gülşah Akdemir, Marije K. Verheul, Lotte Heimans, Kirsten V.C. Wevers-de Boer, Yvonne P.M. Goekoop-Ruiterman, Maikel van Oosterhout, Joop B. Harbers, Casper Bijkerk, Gerda M. Steup-Beekman, Leroy R. Lard, Tom W.J. Huizinga, Leendert A. Trouw, Cornelia F. Allaart

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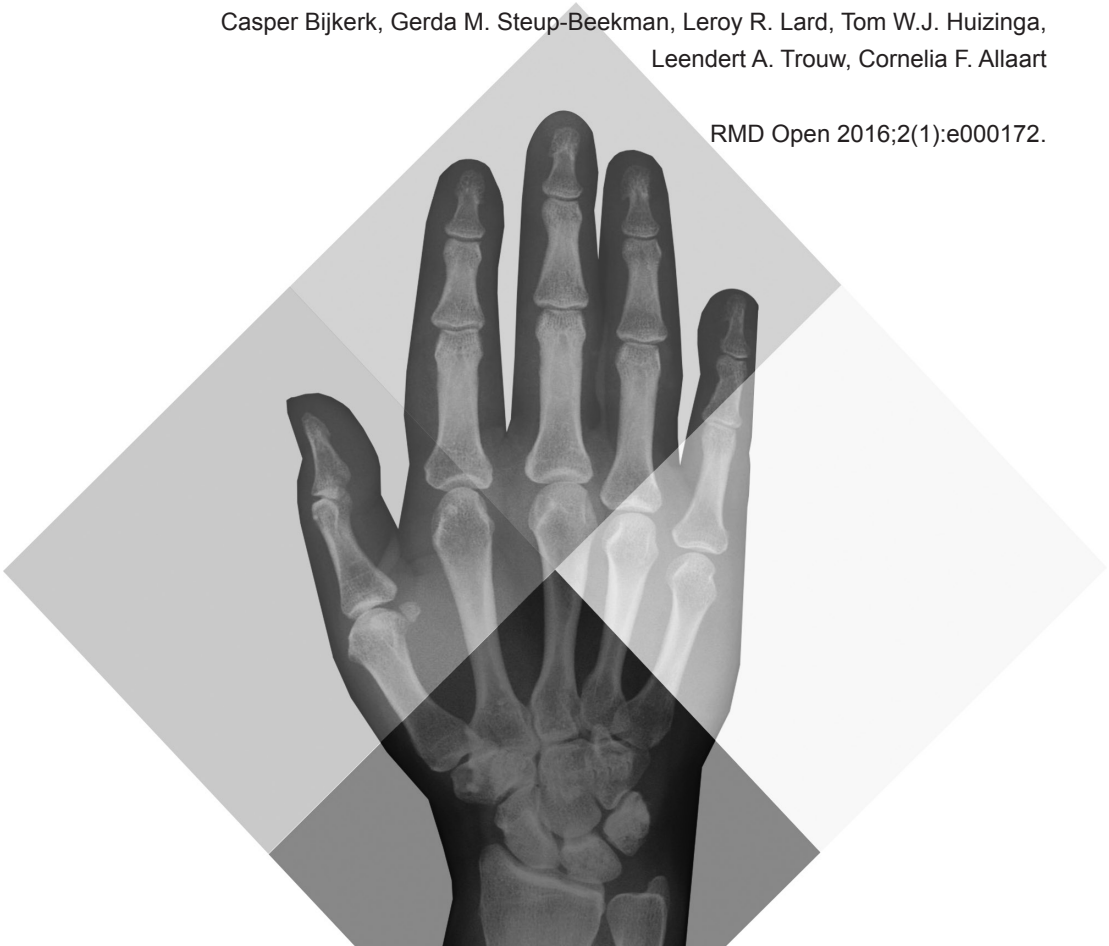

ABSTRACT

Objectives

To identify predictive factors of radiological progression in early arthritis patients treated by remission steered treatment.

Methods

In the IMPROVED study, 610 early rheumatoid arthritis (RA) or undifferentiated arthritis (UA) patients were treated with methotrexate (MTX) and a tapered high dose of prednisone. Patients in early remission (Disease Activity Score (DAS)<1.6 after 4 months) tapered prednisone to zero. Patients not in early remission were randomized to arm 1: MTX plus hydroxychloroquine, sulphasalazine and prednisone or to arm 2: MTX plus adalimumab. Predictors of radiological progression (≥0.5 Sharp/van der Heijde score; SHS) after 2 years were assessed using logistic regression analysis.

Results

Median (IQR) SHS progression in 488 patients was 0 (0-0) point, without differences between RA or UA patients or between treatment arms. In only 50/488 patients SHS progression was ≥0.5: thirty-three (66%) were in the early DAS remission group, nine (18%) in arm 1, five (10%) in arm 2, three (6%) in the outside of protocol group. Age (OR (95% CI) 1.03 (1.00-1.06)) and the combined presence of anti-carbamylated protein antibodies (anti-CarP) and anti citrullinated protein antibodies (ACPA) (2.54 (1.16-5.58)) were independent predictors for SHS progression. Symptom duration <12 weeks showed a trend.

Conclusions

After two years of remission steered treatment in early arthritis patients, there was limited SHS progression in only a small group of patients. Numerically, patients who had achieved early DAS remission had more SHS progression than other patients. Positivity for both anti-CarP and ACPA and age were independently associated with SHS progression.

INTRODUCTION

Rheumatoid arthritis (RA) treatment has considerably changed in the past decades. Earlier treatment with combination therapy and a treat-to-target approach have resulted in earlier and better suppression of inflammation and radiologic progression.[1-7] It is thought that induction of disease activity score (DAS) remission, for which ever stricter criteria are defined, will ensure optimal suppression of disease processes.[8] With joint destruction becoming a rare outcome, it is mainly of pathophysiological interest, which patients remain most at risk for radiologic progression.

Anti-citrullinated protein antibodies (ACPA) positivity in RA is associated with more radiological joint damage and in undifferentiated arthritis (UA) and arthralgia it predicts progression to RA.[9,10] Also, the recently identified anti-carbamylated protein antibodies (anti-CarP) are associated with more radiological progression, specifically in ACPA-negative patients.[9] The presence of anti-CarP predates clinical disease;[11-13] in arthralgia patients it can predict the progression to RA regardless of ACPA status.[10]

In addition, previous research showed that loss of bone mineral density as measured with Digital X-ray Radiogrammetry (DXR-BMD) in the metacarpals using standard hand radiographs in the first 4 months is associated with radiological progression after one year.[14] Local BMD loss occurs early in the disease course and may be caused by increased osteoclast activity caused by inflammation processes.

In the IMPROVED study, we treated patients with early RA and UA, with the aim to induce and maintain clinical remission (DAS<1.6). DAS remission rates were high, and radiological progression low.[7,15] Yet, some patients still developed radiologic progression, and this provides an opportunity to look for factors associated with and potentially driving radiologic progression. Thus, in this post-hoc analysis we aimed to determine which baseline characteristics and 4-month outcomes are associated with joint damage after 2 years of remission steered treatment.

METHODS

Subjects and study design

The IMPROVED study is a multicentre, randomized clinical trial with 610 patients ≥18 years and symptom duration ≤2 years, and not treated with previous antirheumatic therapy, diagnosed with early RA (2010 classification criteria [16]) or UA, defined by at least one inflammatory arthritis and one other painful joint, clinically suspected for early RA according to the treating rheumatologist. Medical Ethics Committees of all participating centres approved the study protocol and all patients gave written informed consent.

All patients started treatment with methotrexate (MTX) 25mg/wk and prednisone tapered from 60mg/day to 7.5 mg/day in 7 weeks. After 4 months patients who achieved a DAS<1.6 (early DAS remission) tapered prednisone to 0. If remission was maintained at 8 months MTX was tapered to 0. Patients not in early DAS remission after 4 months, were randomized to arm 1: MTX, hydroxychloroquine (HCQ), sulphasalazine (SSZ) and prednisone or to arm 2: MTX+adalimumab. If patients in arm 1 were in remission after 8 months, first prednisone, than SSZ and finally HCQ were tapered to 0. Four months later MTX could be tapered to 0 if patients achieved remission. In arm 2, after 8 months adalimumab was tapered to 0 if patients achieved remission and if remission maintained four months later MTX was tapered to 0. Treatment adjustments were made every four months; medication was tapered and next stopped in case of remission but increased or switched in case of no remission. Fifty patients who did not achieve early DAS remission were not randomized as the protocol required and were treated outside of protocol (OP) according to their rheumatologist based on the DAS. Details about the study protocol were previously published.[7] We used data from 488 patients who had full sets of radiographs of hands and feet at baseline and after 2 years. For the other patients either a baseline or 2 year radiograph was missing.

Measurements

Radiological damage was assessed on radiographs of hands and feet annually in random order using the Sharp/van der Heijde score (SHS) as mean of 2 independent readers, blinded for patient identity.[17] Radiological progression was defined as an increase in SHS≥0.5 point. Since only a small group of patients (50/488) showed progression reliability could not be measured by intra-class coefficients.[18] Consensus scores were reached for radiographs with inter-reader difference of ≥2 points progression. Suitable routine digital X-rays of both hands were used to measure DXR-BMD measured by DXR online (Sectra, Linköping, Sweden)[19] at baseline and 4 months. 'DXR-BMD loss' was defined as a loss in DXR-BMD of ≥1.5 mg/cm^2/4 months calculated by subtracting DXR-BMD at 4 months by DXR-BMD at baseline.[14]

Anti-CarP were measured in sera at baseline by Enzyme-Linked Immuno Sorbent Assay (ELISA) using carbamylated FCS in-house as described before.[9] ACPA were determined at baseline using the anti-cyclic citrullinated peptide (anti-CCP2) test.
'Boolean remission' was defined by the 2011 ACR/EULAR remission criteria [8] and was measured after 4 months.

Statistical analysis

For the analysis of continuous data we used the independent t-test and for categorical data χ^2 test. For non-Gaussian data the Mann-Whitney test and χ^2 test were used.

Clinical and radiological predictors at baseline and 4-months outcomes were entered in the univariable logistic regression analysis with SHS progression as binary outcome. Variables with a p-value <0.2 were entered in the multivariable model.
Early DXR-BMD loss showed a p-value <0.2, however this was a variable with almost half missing values due to unsuitability of the X-rays to measure the DXR-BMD. In order to avoid bias and to increase power the variable was imputed using multiple imputation in 442 patients that had at least one DXR-BMD measure.
Anti-CarP and ACPA could not be entered in the same model due to multicollinearity. A combined variable was entered in the model instead. Data was analysed by the statistical program SPSS 20.0.

RESULTS

Clinical characteristics and treatment

After two years, median SHS progression in all groups (early DAS remission, arm 1, arm 2 and OP) and in RA and UA patients was 0 (range 0-22). 50/488 patients (10%) had SHS progression; 33/387 (9%) in early DAS remission, 9/83 (11%) in arm 1, 5/78 (6%) in arm 2, 3/50 (6%) in the OP group (table 1 and figure 1). JSN progression was seen in 23/33 patients in early DAS remission, 9/9 in arm 1, 4/5 in arm 2 and 2/3 in the OP group. Erosion progression was scored in 17/33 patients in early DAS remission, 0 in arm 1, 2 in arm 2 and 1 in the OP group. 8/50 (16%) patients (all RA, 7 in early DAS remission and 1 in arm 2) had ≥5 SHS progression (minimal clinically important difference and smallest detectable difference [20]) (supplementary table 1). 22/50 (44%) patients (20 RA and 2 UA patients, 16 in early DAS remission, 3 in arm 1, 2 in arm 2 and 1 in OP group) had ≥2 SHS progression (smallest detectable change [21]). 10/33 early DAS remission patients with SHS progression were in drug-free remission (DFR) after 2 years. 1/33 patients had ≥5 SHS progression (supplementary table 1).
After 4 months 144 patients (all in early DAS remission) were in 'Boolean remission'. Mean (SD) age in 'Boolean remission' patients was 51.2 (14.3) and in patients not in 'Boolean remission' 51.8 (13.9), p=0.662 (table 2). ACPA positivity 86 (60%) vs. 223 (53%) p=0.106 and anti-CarP positivity 47 (33%) vs. 116 (28%) p=0.166 were similar in both groups. SHS progression was seen in 16/144 (11%) of 'Boolean remission' patients and 31/420 (7%) patients not in 'Boolean remission' (p=0.264). The other 3 patients that had SHS progression had missing data to calculate 'Boolean remission'. Median (IQR) SHS progression was not different in patients in 'Boolean remission' 0 (0-0) and patients not in 'Boolean remission' 0 (0-0), p=0.357.

Table 1: Baseline characteristics and clinical outcomes for the total population, SHS progression and no SHS progression.

	Total population n=488	SHS progression n=50	No SHS progression n=438	p-value
Baseline				
Age (years), mean±SD	51±14	56±12	51±14	0.008
Female, n (%)	333 (68)	33 (66)	300 (68)	0.720
RA (2010), n (%)	388 (80)	41 (82)	347 (79)	0.777
DAS, mean±SD	3.19±0.91	3.25±1.08	3.19±0.89	0.649
HAQ, mean±SD	1.15±0.67	1.09±0.66	1.15±0.67	0.545
Symptom duration in weeks, median (IQR)	18 (9-34)	25 (16-39)	17 (9-32)	0.032
RF positive, n (%)	273 (56)	31 (62)	242 (55)	0.242
ACPA positive, n (%)	274 (56)	35 (70)	239 (55)	0.053
Anti-CarP positive, n (%)	139 (29)	22 (44)	117 (27)	0.012
ESR mm/h (median, IQR)	24 (11-39)	31 (19.5-43.5)	24 (10.8-38.0)	0.020
SJC, median (IQR)	5 (3-10)	5 (2-12)	5 (3-10)	0.921
TJC, median (IQR)	6 (4-10)	5 (4-9)	6 (4-10)	0.263
SHS, median (IQR)	0 (0-0)	1.25 (0-4)	0 (0-0)	<0.001
DXR-BMD* g/cm^2, median (IQR)	0.591 (0.527-0.643)	0.582 (0.479-0.632)	0.593 (0.529-0.642)	0.322
4 months				
DAS, mean±SD	1.49±0.88	1.43±0.93	1.49±0.87	0.607
ACR/EULAR remission, n (%)	125 (26)	16 (32)	109 (25)	0.264
Early DAS remission, n (%)	322 (66)	33 (66)	289 (66)	0.998
Arm 1 DMARD combination, n (%)	69 (14)	9 (18)	60 (14)	0.408
Arm 2 adalimumab, n (%)	65 (13)	5 (10)	60 (14)	0.466
Outside of Protocol, n (%)	32 (7)	3 (6)	29 (7)	0.867
DXR-BMD* g/cm^2, median (IQR)	0.588 (0.522-0.631)	0.579 (0.496-0.646)	0.590 (0.522-0.631)	0.747
2 years				
DAS, mean±SD	1.47±0.83	1.52±0.85	1.47±0.83	0.670
HAQ, mean±SD	0.54±0.60	0.58±0.62	0.53±0.60	0.583
Total SHS, median (IQR)	0 (0-0.5)	4 (1.0-6.6)	0 (0-0)	<0.001
SHS progression, median (IQR)	0 (0-0)	1 (0.5-3.0)	0 (0-0)	<0.001
JSN, n (%)	111 (23)	40 (80)	71 (16)	<0.001
JSN, median (IQR)	0 (0-0)	3 (0.9-6.0)	0 (0-0)	<0.001
JSN progression, n (%)	38 (78)	37 (74)	1 (0.2)	<0.001
JSN progression, median (IQR)	1.8 (0.9-3.0)	1.5 (0.8-3.0)	2 (2-2)	<0.001
Erosive, n (%)	49 (10)	26 (52)	23 (5)	<0.001
Erosion score, median (IQR)	0 (0-0)	0.5 (0-1)	0 (0-0)	<0.001
Erosion progression, n (%)	20 (41)	20 (40)	0 (0)	<0.001
Erosion progression, median (IQR)	0.5 (0.5-3.0)	0.5 (0.5-3.0)	0 (0-0)	<0.001
DAS-remission, n (%)	285 (58)	29 (58)	256 (58)	0.905
Drug-free remission, n (%)	123 (25)	12 (24)	111 (25)	0.822

RA: rheumatoid arthritis; DAS: disease activity score; HAQ: health assessment questionnaire; RF: rheumatoid factore; ACPA: anti-citrullinated protein antibodies; anti-CarP: anti-carbamylated protein antibodies; ESR: erythrocyte sedimentation rate; SJC: swollen joint count; TJC: tender joint count; SHS: Sharp/van der Heijde score; DXR-BMD: metacarpal bone mineral density measured by digital X-ray radiogrammetry; JSN: joint space narrowing; IQR, interquartile range; SD, standard deviation; *: DXR-BMD data imputed in 442 patients.

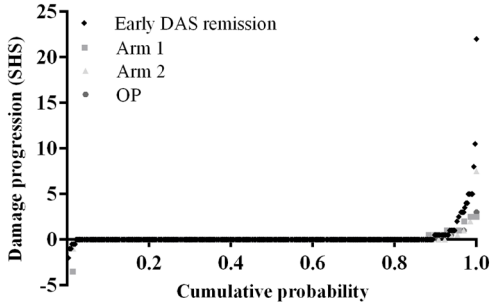

Figure 1: Probability plot of SHS progression over 2 years for the different treatment groups
SHS: Sharp/ van der Heijde score; OP: outside of protocol group

Table 2: Baseline characteristics and clinical outcomes according to 'Boolean remission' measured after 4 months

	'Boolean remission' n=144	No 'Boolean remission' n=420	p-value
Baseline			
Age (years), mean±SD	51.2±14.3	51.8±13.9	0.662
Female, n (%)	89 (62)	290 (69)	0.110
RA (2010), n (%)	114 (79)	327 (78)	0.707
DAS, mean±SD	3.05±0.91	3.28±0.92	0.008
HAQ, mean±SD	1.04±0.67	1.21±0.65	0.007
Symptom duration, weeks, median (IQR)	17 (8.8-34)	17.5 (9-32)	0.784
RF positive, n (%)	88 (61)	228 (54)	0.139
ACPA positive, n (%)	86 (60)	223 (53)	0.106
Anti-CarP, n (%)	47 (33)	116 (28)	0.166
ESR mm/h, median (IQR)	26.5 (11.5-36.8)	24 (11-41)	0.596
SJC, median (IQR)	5 (2.3-10)	6 (3-10)	0.796
TJC, median (IQR)	5 (4-8)	7 (4-11)	<0.001
Total SHS, median (IQR)	0 (0-0)	0 (0-0)	0.714
Early DAS remission 4 months, n (%)	144 (100)	226 (54)	<0.001
Arm 1, n (%)	0 (0)	77 (18)	<0.001
Arm 2, n (%)	0 (0)	71 (17)	<0.001
OP (%)	0 (0)	46 (11)	<0.001
2 years			
DAS, mean±SD	1.11±0.75	1.61±0.83	<0.001
HAQ, mean±SD	0.29±0.44	0.64±0.61	<0.001
Total SHS, median (IQR)	0 (0-0.5)	0 (0-0.5)	0.939
SHS progression, median (IQR)	0 (0-0)	0 (0-0)	0.357
SHS progression, n (%)	16 (11)	31 (7)	0.264
DAS remission, n (%)	103 (72)	186 (44)	<0.001
Drug-free remission, n (%)	51 (35)	72 (17)	<0.001
ACR/EULAR remission, n (%)	67 (47)	63 (15)	<0.001

RA: rheumatoid arthritis; DAS: disease activity score; HAQ: health assessment questionnaire; RF: rheumatoid factor; ACPA: anti-citrullinated protein antibodies; Anti-CarP: anti-carbamylated protein antibodies; ESR: erythrocyte sedimentation rate; SJC: swollen joint count; TJC: tender joint count; SHS: Sharp/van der Heijde score; OP: out of protocol group; IQR, interquartile range; SD, standard deviation

SHS progression

Median (IQR) SHS progression in patients with SHS progression was 1.0 (0.5-3.0); joint space narrowing (JSN) progression 1.5 (0.8-3.0), and erosion progression 0.5 (0.0-1.0). 38/488 patients (30 RA and 8 UA, p=0.831) had JSN progression and 20/488 (19 RA and 1 UA, (p=0.145) had erosion progression. Patients with SHS progression were older (5/50 patients with SHS progression were <45 years vs. 122/438 patients without SHS progression were <45 years, p=0.035), had a longer symptom duration (11/50 symptom duration <12 weeks vs. 146/438, p=0.092, respectively), were more often anti-CarP-positive (p=0.012) and numerically also more often ACPA-positive or RF-positive and had a higher ESR (31/50 ESR >28 mm/hr vs. 183/438, p=0.006, respectively) (table 1).

Anti-CarP

139/488 patients (28%) were anti-CarP-positive, 274/488 (56%) were ACPA-positive, and 273/488 (56%) were RF-positive, 122/488 (25%) were double positive for anti-CarP and ACPA, and 107/488 (22%) were positive for all 3. Double positivity occurred more in RA than in UA patients (table 3). In anti-CarP-positive patients there was no difference between ACPA-positive and ACPA-negative patients in SHS progression (median (IQR) 0 (0-0) vs 0 (0-0), p=0.354). Median (IQR) SHS at baseline and 2 years was comparable between anti-CarP-positive and anti-CarP-negative patients (table 3). Besides, median SHS at baseline was comparable between double positive (0 (0-1)) and ACPA-positive but anti-CarP-negative patients (0 (0-2), p=0.088) and also at 2 years this was comparable 0 (0-0) vs 0 (0-0.5), p=0.073.

Predictors of SHS progression

Univariable predictors for SHS progression after 2 years that were entered in the multivariable model were double positivity for anti-CarP and ACPA (p=0.011), anti-CarP alone (p=0.014) (ACPA alone showed a trend (p=0.056)), age (p=0.009), baseline ESR>28mm (p=0.007), baseline SHS (p=0.041) and symptom duration <12 weeks (showed a trend p=0.096) (table 4). Early DXR-BMD loss was associated with SHS progression (p=0.019), however the imputed variable was not associated (p=0.100) and therefore not entered in the model. Only age (OR (95% CI) 1.03 (1.00-1.06)) and the combination of anti-CarP and ACPA positivity (2.54 (1.16-5.58)) were independent significant predictors (table 4). Symptom duration <12 weeks (0.49 (0.23-1.04)), ESR>28mm (1.90 (0.95-3.81)) and SHS (1.04 (0.98-1.11)) were not significantly associated but were entered in the model because of a probable association with SHS progression.

In an additional multivariable model including only ACPA and not anti-CarP showed that symptom duration, age and ESR were independent significant predictors (data not shown). A model with anti-CarP instead showed that only anti-CarP was the independent predictor (data

not shown). The model with ACPA was a stronger predictor with a R^2 of 0.053 compared to 0.047 for the model with anti-CarP.

Table 3: Baseline characteristics and clinical outcomes according to anti-CarP status

	Anti-CarP positive n=172	Anti-CarP negative n=350	p-value
Baseline			
Age (years), mean±SD	52±13	52±15	0.570
Female, n (%)	116 (67)	238 (68)	0.898
RA (2010), n (%)	162 (94)	254 (73)	<0.001
DAS, mean±SD	3.27±0.91	3.22±0.94	0.624
HAQ, mean±SD	1.12±0.66	1.19±0.65	0.292
Symptom duration, weeks, median (IQR)	17 (8-33)	18 (9-33)	0.517
Symptom duration <12 weeks, n (%)	64 (37)	113 (32)	0.262
RF positive, n (%)	143 (83)	147 (42)	<0.001
ACPA positive, n (%)	150 (87)	134 (38)	<0.001
ESR mm/h, median (IQR)	31 (17-44.8)	21 (10-38)	0.001
SJC, median (IQR)	6 (3-9)	5 (3-10)	0.714
TJC, median (IQR)	6 (4-9)	7 (4-10)	0.540
Total SHS, median	0 (0-0.5)	0 (0-0)	0.361
Early DAS remission 4 months, n (%)	116 (67)	203 (58)	0.038
2 years			
DAS, mean±SD	1.46±0.87	1.51±0.82	0.536
HAQ, mean±SD	0.46±0.57	0.58±0.61	0.064
Total SHS, median (IQR)	0 (0-1.4)	0 (0-0.5)	0.179
SHS progression, median (IQR)	0 (0-0)	0 (0-0)	0.025
SHS progression, n (%)*	22 (13)	22 (6)	0.012
DAS remission, n (%)	88 (51)	170 (49)	0.648
Drug-free remission, n (%)	32 (19)	84 (24)	0.111
ACR/EULAR remission, n (%)	42 (24)	75 (21)	0.489

Anti-CarP: anti-carbamylated protein antibodies; RA: rheumatoid arthritis; DAS: disease activity score; HAQ: health assessment questionnaire; RF: rheumatoid factor; ACPA: anti-citrullinated protein antibodies;; ESR: erythrocyte sedimentation rate; SJC: swollen joint count; TJC: tender joint count; SHS: Sharp/van der Heijde score; IQR, interquartile range; SD, standard deviation; *: the other 6 patients with SHS progression had missing anti-CarP values.

Table 4: Univariable and multivariable logistic regression analysis with SHS progression as binomial outcome variable.

	OR	95% CI	p-value
Univariable analysis			
Age	1.03	1.01-1.06	0.009
Female	0.89	0.48-1.66	0.720
RA	1.12	0.52-2.39	0.777
DAS	1.08	0.79-1.48	0.648
Symptom duration<12 wks	0.55	0.28-1.11	0.096
RF	1.46	0.77-2.75	0.244
Anti-CarP/ACPA:			
Both negative	ref		
Anti-CarP - ACPA +	1.27	0.53-3.05	0.592
Anti-CarP + ACPA -*	0.86	0.10-7.04	0.885
Both positive	2.67	1.26-5.66	0.011
CRP	1.00	0.99-1.01	0.646
ESR>28mm	2.27	1.25-4.15	0.007
SJC	1.02	0.98-1.07	0.338
TJC	0.99	0.93-1.05	0.661
DAS remission 4 months	0.97	0.53-1.79	0.932
Arm 1#	1.80	0.57-5.69	0.317
Arm 2##	0.56	0.18-1.76	0.317
Early ACR/EULAR remission	1.44	0.76-2.74	0.266
SHS	1.10	1.00-1.20	0.041
Erosion score	1.00	1.00-1.02	0.812
JSN score	1.00	1.00-1.00	0.804
Early DXR-BMD loss	1.22	1.03-1.45	0.019
Early DXR-BMC loss, imputed**	1.18	0.97-1.45	0.100
Multivariable analysis			
Age	1.03	1.00-1.06	0.049
Anti-CarP/ACPA:			
Both negative	ref		
Anti-CarP - ACPA +	1.41	0.57-3.46	0.457
Anti-CarP + ACPA -*	1.13	0.13-9.68	0.908
Both positive	2.54	1.16-5.58	0.020
Symptom duration<12wks	0.49	0.23-1.04	0.063
ESR>28mm	1.90	0.95-3.81	0.070
SHS	1.04	0.98-1.11	0.208

RA: rheumatoid arthritis; DAS: disease activity score; wks: weeks; RF: rheumatoid factor; Anti-CarP: anti-carbamylated protein antibodies; ACPA: anti-citrullinated protein antibodies; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; SJC: swollen joint count; TJC: tender joint count; SHS: Sharp/van der Heijde score; JSN: joint space narrowing; DXR-BMD: metacarpal bone mineral density measured by digital X-ray radiogrammetry; OR: odds ratio; CI: confidence interval; *n=16 patients; **DXR-BMD data imputed in 442 patients, #reference category arm 2, ##reference category arm 1.

DISCUSSION

Of 488 early arthritis patients who were treated with induction therapy followed by remission steered treatment, only 50/488 (10%) patients showed SHS progression ≥0.5 after 2 years and only 8 patients showed SHS progression ≥5 which is considered to be the minimal clinically important difference in SHS. We looked at potential predictors of radiologic progression (after 2 years of treatment) in these patients where disease activity was generally low and radiologic progression was generally effectively suppressed because this allowed us to look for factors associated with radiologic progression unconnected to (suppression of) inflammation. This may be relevant for understanding RA phenotypes. It is unlikely that limited SHS progression will become clinically relevant for these patients in the intermediate future.

To determine why this group still shows SHS progression, we investigated associations between baseline characteristics and four months outcomes with SHS progression. We found that SHS progression comprised more of progression of JSN than of progression of erosions. Small numbers prevented us to analyse both forms of progression separately. Independent predictors for total SHS progression were higher age and the combination of anti-CarP and ACPA positivity. In a reverse of an association between higher disease activity and more damage progression, we found more SHS progression in patients who had achieved early (4 months after treatment start) DAS remission, or even early 'Boolean remission'. Although these patients even after drug tapering as required by protocol on average have lower DAS than patients who did not achieve early remission and where medication was intensified, it may be that there was residual inflammation which has triggered SHS progression. Discontinuation of prednisone may also have removed a drug which even without influencing the DAS may prevent damage progression.[22] As supplementary table 1 suggests, discrepancies in clinical response and radiologic damage progression may indicate that in some patients antirheumatic treatment may effectively suppress symptoms of inflammation, while the underlying processes driving joint destruction may still be present.

Although for most patients treated aiming at DAS remission SHS progression may be a clinically irrelevant finding, for some patients initial SHS progression will still result in later permanent disability,[23] requiring tailored treatment decisions. In addition, identifying risk factors for SHS progression in this population may point towards underlying mechanisms and possibly new drug targets.
Small numbers limited our choice of analyses and interpretation of results. Since both ACPA and anti-CarP have been shown to be related with SHS progression in other RA cohorts, it is likely that this combination of risk factors indicate a RA phenotype with a bad prognosis for joint damage. Because there were few patients with anti-CarP but negative ACPA, we

could not test which of the antibodies was the stronger predictor. However, it appears that in this early and progressively treated patient group, presence of ACPA is a risk factor for SHS progression, but only if anti-CarP was also present. Although data in animal studies suggested a direct effect of human ACPA on osteoclastogenesis, several questions remain open regarding the biochemical nature of ACPA and the specificities involved.[24] The effects of anti-CarP in joint destruction on such a mechanistic level is currently unknown but epidemiological studies show a clear association between anti-CarP and joint destruction especially in the ACPA negative patients.[9,11] Also with regard to double positivity of anti-CarP and ACPA the diagnostic value was clear with high OR for RA. As ACPA and anti-CarP can bind to different antigens,[13] it is possible that especially the combined presence is sufficient to drive bone destruction. However, even though mice can harbour anti-CarP antibodies,[25] experimental evidence to indicate a pathological role for anti-CarP is still lacking.

We found age to be a predictor of SHS progression. As we found that SHS progression was dominated by JSN progression rather than erosion progression in these patients, some JSN progression may represent primary hand osteoarthritis. This was also previously suggested in a study by Khanna et al.[26]

Short symptom duration showed a trend as a protective factor, but possibly due to small numbers, this was not statistically significant. It is also possible that the intensive remission steered treatment in all patients obscured potential advantages of early treatment start. Previous research indicates that shorter symptom duration in RA is associated with less SHS progression.[27,28] SHS progression occurred numerically more often in RA patients than in UA patients. This corroborates the FINRA-Co and NEORA-Co findings, which included not UA but only RA patients, who despite remission steered treatment showed more SHS progression than the IMPROVED patients. It may also reflect that classification as RA according to the 2010 classification criteria, used in our study, can rest strongly on the presence of ACPA.

It was not possible to calculate progression in 122 patients due to missing radiographs at baseline or at 2 years. Of these 122 patients, 79 were lost to follow up and 43 patients had missing radiographs while they were in the study. We could not detect systematic errors concerning these missing radiographs and therefore consider that we have analysed a considerable part of the data.

A threshold for SHS progression of 0.5 seems clinically irrelevant. The majority of our patients had ‘zero progression’. Only a small group had progression with a small range. This damage progression is at least pathophysiologically of interest. JSN that is scored may represent OA mechanisms in our patients, which we also found as a result of our regression analysis.

Finally, SHS progression appeared slightly higher in patients who had achieved early DAS remission. By protocol patients were required to taper and eventually discontinue all DMARDs when DAS remission was achieved, but had to restart as soon as DAS remission was lost. Previously, we found no radiologic damage progression in RA patients who had drug free

remission in the BeSt study, regardless of whether drug free remission was lost or not.[29] Compared to the IMPROVED patients, however, BeSt patients had tapered medication over a long period of low disease activity and subsequent remission before the last DMARD was stopped. In the current study, initiated in 2007, tapering and drug discontinuation was done more quickly as we also included UA patients some of whom could have had a self-limiting, non-damaging type of arthritis. It is possible that if DMARDs are discontinued too quickly, RA disease activity is not sufficiently suppressed, allowing SHS progression in some patients. Studies involving imaging techniques in patients who are in clinical remission also suggest that residual inflammation may be present, which can be associated with subsequent damage progression.[30-32] In our study we did not perform additional imaging to detect this residual subclinical disease. The 2010 EULAR recommendations advise to taper DMARDs slowly only in patients with stable remission, and discontinuation of DMARDs is not encouraged, although it is considered to be an option in some patients. However, we found that DFR was achieved in similar percentages of patients who had achieved early DAS remission with or without SHS progression. To continue treatment when patients are in DAS remission might prevent further SHS progression, but without clear clinical benefits this probably would entail overtreatment with unnecessary (risks of) side effects.

In conclusion, after two years of remission steered treatment in early arthritis patients who started induction therapy, minimal SHS progression occurs in a small group of patients. Independent predictors for SHS progression were age (associated with JSN possibly related to osteoarthritis) and the combination of anti-CarP and ACPA positivity, which appears to represent a phenotype with particularly bad prognosis, even when suppression of inflammatory activity by remission steered treatment prevents damage in other patients. Further research may show whether previous associations of presence of ACPA with bad outcomes of arthritis rests with mechanisms related to ACPA itself, presence of both ACPA and anti-CarP, or mainly with anti-CarP.

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SUPPLEMENTARY FILE

Supplementary table 1: Treatment steps during 2 years of follow up in patients with SHS progression n=50

Patient	Progression score	Treatment group	RF	ACPA	Anti-CarP	DAS 8 mths	Treatment step	DAS 12 mths	Treatment step	DAS 16 mths	Treatment step	DAS 20 mths	Treatment step	DAS 24 mths
1	0.5	ER	-	+	-	0.59	MTX tapered to 0	2.04	Restart MTX	1.69	MTX monotherapy	2.03	Restart prednisone	0.59
2	0.5	Arm 2	missing	-	-	3.16	Increase dose adalimumab	2.42	MTX + adalimumab	ND	ND	1.82	MTX + adalimumab	1.15
3	0.5	ER	-	-	-	0.79	Restart prednisone	1.90	Prednisone tapered to 0	3.10	Randomization: start adalimumab	1.02	Adalimumab tapered to 0	ND
4	0.5	ER	-	-	missing	0.95	MTX tapered to 0	1.18	DFR	0.96	DFR	0.99	DFR	ND
5	0.5	Arm 1	-	-	-	1.66	DMARD combination	2.22	DMARD combination tapered to 0, switch to adalimumab	2.41	Increase dose adalimumab	2.54	Step unclear	1.96
6	0.5	Arm 1	-	-	+	1.36	DMARD combination	1.33	DMARD combination tapered to 0	1.35	MTX decrease dose	1.59	MTX decrease dose	1.19
7	0.5	ER	+	+	-	0.47	MTX tapered to 0	1.54	DFR	4.54	Restart MTX	1.16	MTX monotherapy	1.14
8	0.5	ER	+	+	+	0.67	MTX tapered to 0	1.82	Restart MTX	1.70	Restart prednisone	1.75	Randosmization: start adalimumab	1.55
9	0.5	ER	+	+	+	0.25	MTX tapered to 0	0.26	DFR	0.03	DFR	0.27	DFR	1.01
10	0.5	OP	+	+	-	3.23	Start SSZ monotherapy	2.44	SSZ was stopped short after 8 mths: DFR	1.35	DFR	2.74	DF no remission	2.04
11	0.5	ER	+	+	+	0.99	MTX tapered to 0	1.73	MTX restart	1.79	Restart prednisone	1.03	Prednisone tapered to 0	1.44
12	0.5	ER	+	+	-	1.07	MTX decreased dose	1.30	MTX monotherapy	1.25	MTX decreased dose	0.56	MTX decreased dose	1.32
13	0.5	Arm 2	+	+	-	2.11	Increase dose adalimumab	2.01	MTX + adalimumab	1.59	MTX + adalimumab	0.90	Decrease dose adalimumab	1.88
14	0.5	Arm 1	-	-	-	3.07	DMARD combination tapered to 0, switch to adalimumab	1.97	MTX + adalimumab	3.11	Increase dose adalimumab	3.32	Stop adalimumab, MTX monotherapy	2.37
15	0.5	ER	-	-	-	0.79	MTX tapered to 0	1.56	Restart MTX	1.52	MTX monotherapy	0.62	MTX monotherapy	0.54
16	0.5	ER	-	-	-	1.39	MTX tapered to 0	1.59	DFR	0.62	DFR	0.76	DFR	1.11
17	0.5	ER	-	-	missing	0.24	MTX tapered to 0	0.78	DFR	1.21	DFR	1.28	DFR	1.50
18	0.5	ER	+	+	missing	1.16	Restart prednisone	0.43	Prednisone tapered to 0	1.50	MTX tapered to 0	3.20	Restart MTX + prednisone and start HCQ	0.75

19	1	OP	+	+	-	0.95	MTX decreased dose	1.58	MTX decreased dose	1.19	MTX decreased dose	1.01	MTX tapered to 0	1.06
20	1	ER	-	-	-	0.78	MTX tapered to 0	3.66	Restart MTX	1.74	Restart prednisone	0.88	Prednisone tapered to 0	0.88
21	1	Arm 2	+	+	+	1.84	Increase dose adalimumab	1.71	Decrease dose adalimumab	2.44	TAR: Stop adalimumab + prednisone bridging	2.40	TAR: start etanercept + MTX + prednisone	1.70
22	1	ER	+	+	+	0.82	MTX tapered to 0	3.30	Restart MTX	1.87	MTX montotherapy	2.73	MTX monotherapy	1.79
23	1	Arm 1	+	+	-	0.99	Combination therapy tapered to 0	3.73	Restart MTX + prednisone	2.46	Switch to adalimumab	2.07	Increase dose adalimumab	1.09
24	1	Arm 1	-	-	-	1.86	Combination therapy	1.93	Combination tapered to MTX monotherapy	2.41	MTX monotherapy	1.54	MTX tapered to 0	2.43
25	1	ER	+	+	+	0.80	MTX tapered to 0	0.81	DFR	4.00	Restart MTX + prednisone	0.59	Prednisone tapered to 0	0.73
26	1	ER	+	+	+	2.27	Restart MTX	0.96	MTX monotherapy	0.86	MTX tapered to 0	1.62	DF no remission	2.90
27	1	ER	+	+	-	0.61	MTX tapered to 0	0.61	DFR	1.34	DFR	1.20	DFR	0.73
28	1	Arm 1	-	-	-	2.39	DMARD combination tapered to 0, switch to adalimumab	2.20	Increase dose adalimumab	2.08	MTX + adalimumab tapered to 0	2.08	DFR	1.21
29	2	Arm 1	missing	+	missing	2.21	DMARD combination tapered to 0, switch to adalimumab	1.04	MTX + adalimumab. Extra visit: increase dose adalimumab	1.60	MTX + adalimumab	1.77	MTX + adalimumab	2.04
30	2	ER	+	+	+	2.14	Switch to SSZ, continue prednisone	1.37	Prednisone tapered to 0	1.07	SSZ monotherapy	1.94	Increase dose SSZ	2.41
31	2	Arm 2	+	+	+	1.58	MTX + adalimumab	2.30	Increase dose adalimumab	0.35	MTX + adalimumab	0.27	MTX + adalimumab	0.71
32	2.5	Arm 1	+	+	+	3.75	DMARD combination tapered to 0, switch to adalimumab	2.48	Increase dose adalimumab	2.36	Stop adalimumab, start abatacept	1.05	MTX + abatacept	3.35
33	2.5	ER	+	+	+	0.88	MTX tapered to 0	1.37	DFR	1.65	DF no remission	0.78	DFR	0.99
34	2.5	ER	+	+	+	2.09	Restart prednisone	2.09	MTX monotherapy	2.22	MTX tapered to 0	3.00	DF no remission	1.82
35	2.5	Arm 1	+	+	+	2.67	DMARD combination tapered to 0, switch to adalimumab	2.28	Adalimumab stopped due to AE	2.09	MTX + adalimumab	1.75	MTX + adalimumab	2.56
36	3	ER	-	-	-	0.77	MTX tapered to 0	0.23	DFR	0.83	Restart MTX	1.56	MTX monotherapy	1.34

37	3	ER	+	+	+	2.81	Restart prednisone. Extra visit: randomization: start adalimumab	3.01	Increase dose adalimumab	3.73	Stop adalimumab	3.07	TAR: MTX + start tocilizumab	4.22
38	3	OP	-	+	+	1.02	Restart MTX	2.94	MTX monotherapy	1.78	Restart prednisone	2.28	Prednisone tapered to 0	2.43
39	3	ER	+	+	+	2.32	Restart prednisone	0.97	Prednisone tapered to 0	1.16	MTX tapered to 0	2.10	Restart MTX	1.73
40	3.5	ER	-	-	-	2.92	Restart prednisone	1.45	Prednisone tapered to 0	1.04	MTX tapered to 0	1.62	DFR	0.95
41	4	ER	+	+	+	1.71	Restart Prednisone	1.19	Prednisone tapered to 0	1.44	MTX tapered to 0	1.40	DFR	1.37
42	4	ER	+	+	missing	1.14	MTX tapered to 0	0.46	DFR	0.46	DFR	0.46	DFR	0.36
43	5	ER	missing	+	+	1.76	Restart prednisone	0.55	Prednisone tapered to 0	1.70	Randomization arm 2: start adalimumab	0.46	Adalimumab tapered to 0. MTX continued	0.38
44	5	ER	+	+	+	1.73	Restart prednisone	1.79	Prednisone tapered to 0	2.67	Randomization arm 2: start adalimumab	ND	Extra visit: increase dose adalimumab. TAR: start etanercept + prednisone	3.48
45	5	ER	+	+	missing	2.11	MTX stopped due to AE: DF	1.88	Restart MTX + prednisone	0.85	MTX continued. Prednisone tapered to 0	0.69	MTX monotherapy	0.91
46	5	ER	-	-	-	0.94	MTX tapered to 0	0.94	DFR	0.75	DFR	0.89	DFR	0.89
47	7.5	Arm 2	+	+	-	1.71	Increase dose adalimumab	1.23	Decrease dose adalimumab. Extra visit: increase dose adalimumab	3.48	TAR: start etanercept + MTX	0.80	TAR: start etanercept + MTX	0.86
48	8	ER	+	+	+	1.00	MTX tapered to 0	1.04	DFR	0.89	DFR	1.64	DF no remission	0.26
49	10.5	ER	+	+	-	1.56	Restart prednisone	0.93	Prednisone tapererd to 0	1.45	MTX tapered to 0	1.90	Restart MTX	1.80
50	22	ER	+	+	+	4.04	Extra visit after 4 mths: randomization: start adalimumab. OP: persistent activity. Start DMARD combination.	3.81	Prednisone + MTX + etanercept	2.52	Prednisone + MTX + etanercept	2.55	Prednisone + MTX + etanercept	2.11

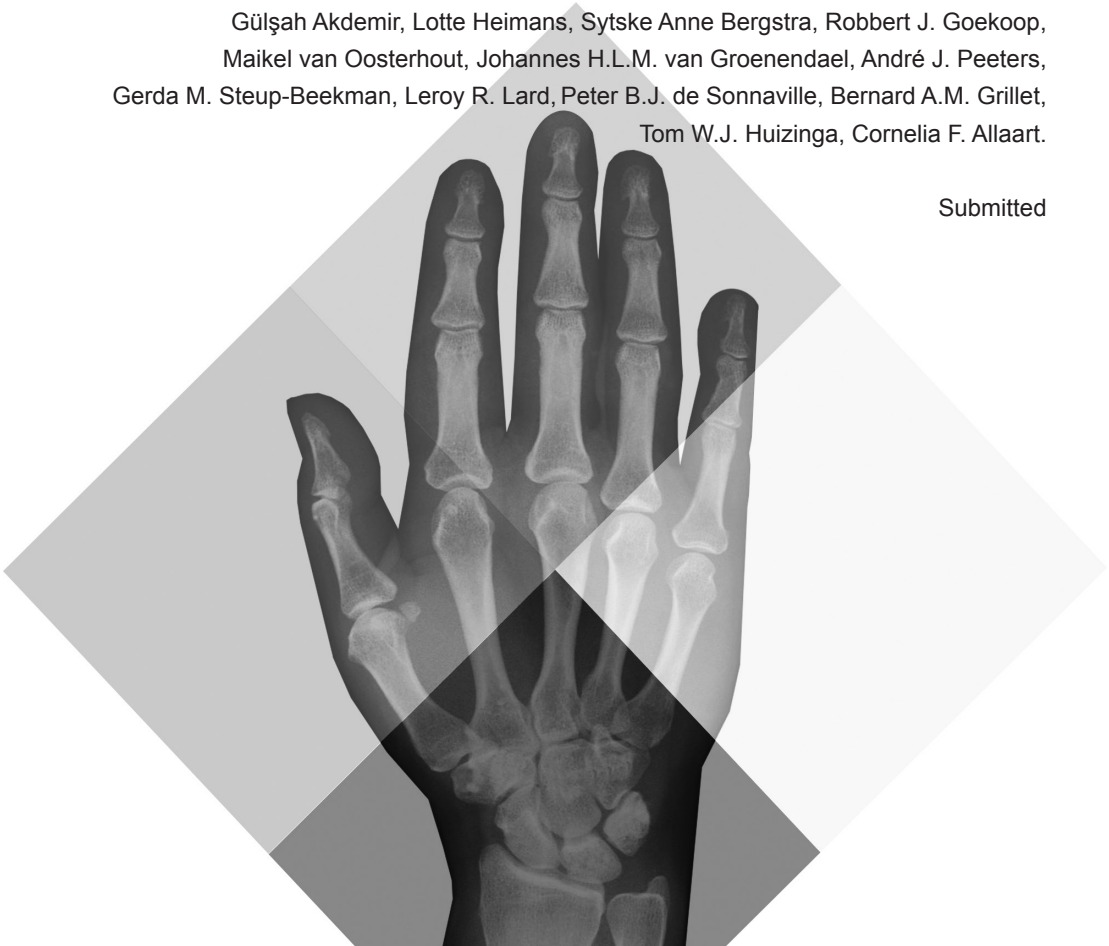
DAS: disease activity score; mths: months; ER: early DAS remission; OP: out of protocol; RF: rheumatoid factor; ACPA: anti-citrullinated protein antibodies; Anti-CarP: anti-carbamylated protein antibodies; +: positive; -: negative; MTX: methotrexate; DMARD: disease modifying antirheumatic drugs; SSZ: sulphasalazine; HCQ: hydroxychloroquine; DFR: drug-free remission; AE: adverse event; TAR: treatment according to rheumatologist; ND: not done.

Chapter 4

REMISSION INDUCTION THERAPY FOLLOWED BY TWO TREATMENT STRATEGIES AIMED AT DRUG-FREE REMISSION IN PATIENTS WITH EARLY ARTHRITIS: FIVE YEAR RESULTS OF A MULTICENTRE, RANDOMISED SINGLE-BLIND CLINICAL TRIAL (THE IMPROVED-STUDY)

Gülşah Akdemir, Lotte Heimans, Sytske Anne Bergstra, Robbert J. Goekoop, Maikel van Oosterhout, Johannes H.L.M. van Groenendael, André J. Peeters, Gerda M. Steup-Beekman, Leroy R. Lard, Peter B.J. de Sonnaville, Bernard A.M. Grillet, Tom W.J. Huizinga, Cornelia F. Allaart.

Submitted



SUMMARY

Background
Early treatment start and earlier introduction of biologic therapies in rheumatoid arthritis (RA) may ensure that early sustained drug-free remission (DFR) can be achieved.

Methods
In 12 hospitals, 610 early (<2 years) RA or undifferentiated arthritis (UA) patients were included in a randomised, single-blinded clinical trial. All patients started methotrexate (MTX) 25mg/week and prednisone (60mg/day tapered to 7.5mg/day). Patients **not** in early DAS-remission (Disease Activity Score <1.6 after 4 months) were randomized to arm 1: adding hydroxychloroquine 400mg/day and sulphasalazine 2000mg/day, or arm 2 switching to MTX plus adalimumab 40mg/2weeks. Treatment adjustments over time aimed at DFR. Outcomes were DAS-remission percentages, functional ability, toxicity and radiologic damage progression after five years.

Results
After four months, 387 patients were in early DAS-remission, 83 were randomised to arm 1 and 78 to arm 2. After five years, 295/610 (48%) patients were in DAS-remission, 26% in sustained (≥ 1 year) DFR. In the early DAS-remission group 220/387 (57%) were in DAS-remission and 135/387 (35%) in sustained DFR. Between the randomization arms clinical outcomes were comparable, (50% in DAS-remission, 12% in sustained DFR). Overall, mean HAQ was 0.6 (SD 0.5)), and damage progression was low (median progression 0.5 (0-2.7) Sharp/vanderHeijde points).

Conclusions
Five years of DFR steered treatment in early arthritis patients results in almost normal functional ability without clinically relevant joint damage across treatment groups. Patients in early DAS-remission had the best clinical outcomes. There were no differences between the randomization arms. Sustained DFR is a realistic treatment goal.

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disorder characterized by inflammation of synovial joints.[1] Uncontrolled inflammation can lead to destruction of affected joints, which can occur before symptoms meet the classification criteria (undifferentiated arthritis, UA), and vasculitis with organ damage.[1-3] In the last decades the therapeutic approach of RA has changed drastically, starting with Disease Modifying Antirheumatic Drugs (DMARD) as soon as possible, in particular in combination with a course of corticosteroids or a biologic DMARD, and intensifying or changing medication as long as a predefined target of disease activity has not yet been achieved.[4-13] Achievement of remission (disease activity score (DAS)<1.6) appears to be a realistic goal in these patients and even drug-free remission is feasible.[4, 8] Sustained drug-free remission can be used as an analogue for cure, although a disease flare may occur which warrants restart of medication. There is evidence that the chance of a flare is reduced if treatment is started very early, possibly before the disease characteristics meet classification criteria.[12]

In the IMPROVED-study we aimed at early drug-free remission in early RA and UA patients. All patients started with induction therapy with methotrexate (MTX) and a tapered high dose of prednisone. As long as DAS-remission was not achieved, every four months the medication was intensified according to two randomisation arms with variations in the order of use of DMARDs. Drug tapering was required when DAS-remission was achieved, but medication was increased or restarted when DAS-remission was lost. Here we report five years clinical and radiological outcomes of induction therapy followed by DAS-remission steered treatment in the two randomisation arms as well as in the total group.

METHODS

Study design

The IMPROVED-study (acronym for Induction therapy with MTX and Prednisone in Rheumatoid Or Very Early arthritic Disease) is a multicentre, two-step randomised, single-blinded, clinical trial designed by Dutch rheumatologists participating in the Foundation for Applied Rheumatology Research (FARR). The general aim was to achieve clinical remission (Disease Activity Score <1.6) as early as possible, with initial combination therapy, followed, for patients not in DAS-remission at four months, by two strategies of medication use, either switching immediately to a biologic DMARD or first trying additional synthetic DMARDs. All patients were required to taper and stop medication if and as long as DAS-remission was achieved. The study was conducted in 12 hospitals in the Western part of the Netherlands. The study protocol was approved by the Medical Ethics Committee of each participating centre.

Patients

Eligible patients were ≥18 years, with early RA fulfilling the 2010 American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) classification criteria[5] with a symptom duration ≤2 years, or UA suspected to be early RA according to the rheumatologist, regardless of symptom duration, with a DAS≥1.6, who had not been treated with prednisone and/or DMARDs. Exclusion criteria were pregnancy or wish to become pregnant during the study, malignancy within the last five years, bone marrow hypoplasia, aspartate transaminase (AST) and/or alanine transaminase (ALT) >3 times normal value, serum creatinine level >150umol/l or estimated creatinine clearance <75%, uncontrolled diabetes mellitus, uncontrolled hypertension, heart failure (New York Heart Association class III/IV), alcohol or drug abuse, serious infections in the previous three months or chronic infectious disease, active or latent hepatitis B infection, known HIV infection, lymphoproliferative disease and multiple sclerosis.[7, 13] Patients with active tuberculosis (TB) and UA patients with latent TB were excluded. RA patients with latent TB could be enrolled if they started adequate antituberculous therapy prior to initiation of high dose prednisone, according to local recommendations. All patients gave written informed consent.

Intervention

During the first four months all patients were treated with MTX 7.5 mg/week increased to 25 mg/week in 5 weeks (or highest tolerated dose, oral or subcutaneous at the discretion of the rheumatologist) and prednisone tapered in seven weeks from 60 mg/day to 7.5 mg/day. The DAS (based on an evaluation of 53 joints for tenderness and 44 joints for swelling, ESR and patient's assessment of global health on a 100 mm Visual Analogue Scale)[11] was assessed every four months. A DAS<1.6 was considered to denote DAS-remission.[9] For all patients over five years, if the DAS was ≥1.6, dose intensification or a drug change or restart of last discontinued medication was required, and medication was tapered to 0 as soon as and as long as DAS was <1.6, until drug-free remission was achieved.

Patients who were in DAS-remission after four months (early DAS-remission) tapered and after three weeks stopped prednisone, then, if DAS-remission continued at eight months, over ten weeks tapered and stopped MTX, thus achieving drug-free remission at year one (supplementary figure 1). If, at eight months, DAS had increased to ≥1.6 prednisone was restarted at 7.5 mg/day. With regained DAS-remission, this could be tapered and stopped again, but with persistent or recurrent DAS≥1.6, 'delayed randomisation' (in the arms as below) was required. They, as patients not in early DAS-remission, continued treatment according to one of two randomisation arms:

In arm 1 patients were treated with MTX (25 mg/week or highest tolerated dose), sulphasalazine (SSZ) 2000 mg/day, hydroxychloroquine (HCQ) 400 mg/day and prednisone 7.5 mg/day. If DAS-remission was achieved, first prednisone, then SSZ, then HCQ were tapered and

stopped, followed by tapering and discontinuation of MTX if DAS-remission remained four months later. Medication was restarted if DAS-remission was lost. If DAS-remission was not achieved, medication was changed to MTX and adalimumab 40 mg/2 weeks, which subsequent treatment steps as in arm 2. Patients in arm 2 received adalimumab at four months, tapering and stopping prednisone in three weeks and continuing MTX. In both arm 1 and arm 2, if DAS-remission was not achieved on adalimumab plus MTX, adalimumab was increased to 40 mg/week. If DAS-remission was still not achieved, subsequent treatment steps were left to shared decision making by rheumatologist and patient.
Fifty patients who did not achieve DAS-remission at four months who were incorrectly not randomised (protocol violation) were followed in the Outside of Protocol (OP) group.

Primary and secondary outcomes

Data of all centres were centrally assessed. Primary outcomes after five years were percentages of DAS-remission and drug-free remission based on a DAS<1.6, or on the proposed DAS-remission definition published by the ACR/EULAR in 2011 (Boolean).[6] 'Sustained drug-free remission was defined by drug-free remission during ≥1 year, starting at any time point. 'Early sustained drug-free remission' was defined by a subsequent period of ≥1 year of drug-free remission beginning at the first possibility to achieve drug-free remission at t=12 months, which was only possible in the early DAS-remission patients.
Secondary outcomes were mean DAS, mean functional ability assessed by the Dutch version of the Health Assessment Questionnaire (HAQ),[10] radiological damage progression of the joints in hands and feet, and toxicity. Baseline and annual radiographs of hands and feet, blinded for patient identity and treatment allocation, were scored for the presence of erosions and joint space narrowing using the Sharp-van der Heijde score (SHS)[214], by two trained, independent readers (GA and SB) in chronological order. The mean of both readers' score was used, unless there was disagreement >2 points, in which case the radiographs were rescored in consensus (n=82 patients). Progression ≥0.5 or ≥5 points[15] was reported and compared between groups. Prior to scoring the IMPROVED radiographs, a sample of 35 patients from the BeSt-study[16] with baseline and five year annual radiographs of hands and feet were scored in chronological order blinded for patient identity and treatment allocation, and an intra-class correlation coefficient ICC[17] calculated to measure reliability between the readers: this was 0.97. Due to the small number of patients with damage progression, ICC in the IMPROVED-study could not be determined.
In patients with available baseline and five year radiographs the progression score over five years was calculated. Missing values for annual erosion and narrowing scores of hands and feet were imputed by multiple imputation, after first log-transformation because of skewed data, with age, gender, symptom duration, body mass idex (BMI), smoking status, diagnosis, autoantibody status (rheumatoid factor (RF), anti-citrullinated protein antibodies (ACPA)

and anti-carbamylated protein antibodies (anti-CarP)), baseline DAS and HAQ, as well as allocated treatment strategy, annual DAS and HAQ and log-transformed annual erosion and joint space narrowing scores of hands and feet added in the imputation model.
Signs and symptoms of adverse events were recorded through unstructured open end questioning by the research nurses at each four-monthly visit in the first two years and afterwards annually, and/or by the treating physician, and coded by the trial physician. Serious adverse events were reported to the study centre within 24 hours of occurrence. (Serious) Adverse events were reported per 100 patient years.

Statistical analysis

The target sample size was calculated with a power calculation to detect differences between randomisation arms of at least 50% in DAS-remission rates and 0.2 points in HAQ with a power of 80%. Based on an estimated 30% of the patients achieving early DAS-remission we would need 535 patients to randomise 100 patients in each arm. During the study more patients achieved early DAS-remission and the target sample size was recalculated and increased to 610 patients. Comparisons in outcomes were made between the randomisation arms. In addition, outcomes were compared across the whole cohort in relation to drug-free remission steered treatment, for baseline characteristics such as disease activity, autoantibody status and symptom duration.
Outcomes were compared 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 a Toeplitz heterogenous covariance structure (DAS), and unstructured covariance structure (HAQ). We performed intention-to-treat analyses. All statistical analyses were conducted with SPSS for Windows version 23·0.
The study is registered with the **ISRCTN Register, number** 11916566 and EudraCT number 2006-006186-16.

RESULTS

Between March 13, 2007 and September 24, 2010, we assessed 730 patients, of which 120 were ineligible and 610 were included in the study (figure 1). Of the 610 patients, 479 (79%) had classifiable RA and 131 (21%) UA (including nine patients who could not be classified because of missing information on symptom duration and/or ACPA/RF status). During five years of the study 152/610 (25%) patients (112 with RA, 40 with UA) were lost to follow-up: 17 patients died, 13 left the study due to comorbidity, 12 had a revised diagnosis and 110 withdrew consent. Twelve patients left the study before the first assessment at four months. Of 610 patients, 387 (63%) achieved early DAS-remission, 375 (61%) at four months, 12

(2%) more after a reassessment 4-6 weeks later (per protocol because the rheumatologists disagreed with the DAS at four months). One-hundred-sixty-one of 610 patients (26%) were randomised; 83 patients to arm 1, and 78 to arm 2. Fifty patients not in early DAS-remission were not randomised (protocol violation) and were analysed in the OP group. Baseline characteristics were well balanced between the randomisation arms.

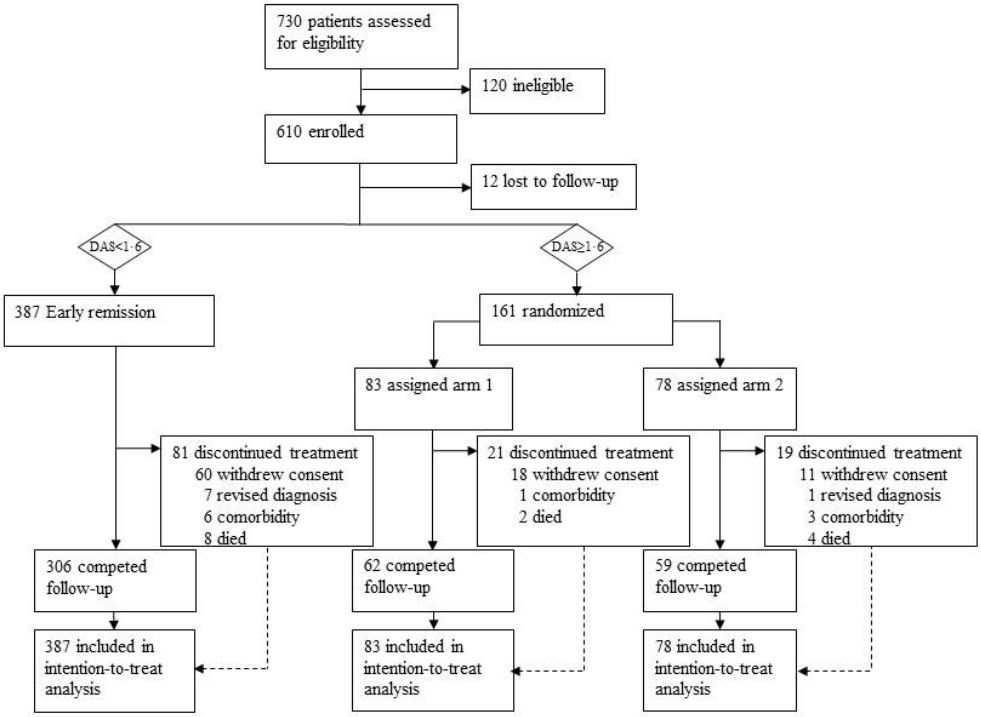


Figure 1. Trial profile IMPROVED-study
First DAS evaluation was at four months. Fifty patients who were not in DAS-remission at four months but were not randomized according to the protocol, were treated outside of protocol (OP group). Of those, nineteen discontinued treatment before five years and 31 patients were included in the intention-to-treat analysis.

General outcomes of the whole group

Baseline characteristics of all patients in the study are shown in table 1. Six patients never achieved DAS-remission during five years follow-up. All others achieved DAS-remission at least once. Over five years, 295/610 patients (48%) were in DAS-remission and 137/610 (22%) were in ACR/EULAR Boolean remission. Of those 295 in DAS-remission, 159 (26% of 610) were in sustained (≥1 year) drug-free remission. Of those 159, 58 had achieved drug-free remission from year one (i.e. early sustained drug-free remission), and of those 58, 24

(4% of 610) were still in drug-free remission at five years. Twenty-six had lost DAS-remission and restarted medication, and eight had left the study early, while still in drug-free remission. Patients in or not in DAS-remission had clinically relevant differences [13] in functional ability: mean difference in HAQ was -0.4 (95% confidence interval -0.5;-0.3) and mean difference in DAS -0.4 (-0.6;-0.3) between patients in or not in DAS-remission at five years.

After five years, radiographs at baseline and five years were available in 362/610 patients (362/458 of patients still in the study after five years). SHS progression ≥0.5 points was seen in 180/458 (39%) of completers, with a median SHS progression (interquartile range) of 0 (0-3) points. 58/458 (13%) had progression ≥5. Mean yearly progression rates were 0.43 points/year, in all completers.

During five years of follow-up 555 (91%) patients had in total 2897 adverse events (AE) (21.4 AE per 100 patient years (supplementary table 2)). The most common AE were upper airway infections, increased liver enzymes and skin rash. 148 (24%) patients reported 242 serious (S)AEs (5.7 SAE per 100 patient years).

Table 1. Baseline characteristics of the IMPROVED-study population.

	Total population
	n = 610
DAS, mean ± SD	3.2 ± 0.9
HAQ, mean ± SD	1.2 ± 0.7
Age in years, mean ± SD	52 ± 14
Female, n (%)	414 (68)
Symptom duration (weeks), median (IQR)	18 (9-32)
RF positive, n (%)	339 (56)
ACPA positive, n (%)	333 (55)
Anti-CarP positive, n (%)	172 (28)
Fulfilled RA(2010) classification criteria, n (%)	479 (79)
Swollen Joint Count, median (IQR)	5 (3-10)
Tender Joint Count, median (IQR)	6 (4-9)
ESR mm/hr, median (IQR)	25 (11-39)
VAS global health (mm), mean ± SD	46 ± 23
Total SHS, median (IQR) (observed)	0 (0-3)
Total SHS, median (IQR) (after imputation)	0.5 (0-3)
Erosive, n (%) (observed)	73 (12)
Erosive, n (%) (after imputation)	79 (13)

DAS: disease activity score; HAQ: health assessment questionnaire; RF: rheumatoid factor; ACPA: anti-citrullinated protein antibodies; RA: rheumatoid arthritis; Anti-CarP: anti-carbamylated protein antibodies; ESR: erythrocyte sedimentation rate; VAS: visual analogue scale; SHS: Sharp-van der Heijde score; Erosive: ≥1 erosions; n: number.

Comparisons between patients in and not in early DAS-remission

Patients who achieved early DAS-remission had at baseline lower DAS (mean (SD) 3.0 (0.8) compared to 3.6 (0.9) in patients who were not in early DAS-remission and HAQ (1.0 (0.7)

compared to 1.4 (0.6) (supplementary table 1), which may explain why the DAS-threshold of 1.6 was more readily achieved. Still, HAQ improvement over time was similar as in the other patients (-0.6 (0.7) in the early DAS-remission group and -0.5 (0.8) in the other patients (figure 2A), resulting in mean HAQ over time over 0.4 (0.4) and 0.9 (0.5), respectively. Also, symptom duration was slightly less in the early DAS-remission group, and fewer patients in the early DAS-remission group were female. On the other hand, slightly less fulfilled the classification criteria for RA, however more were positive for autoantibodies, and more had erosions on radiographs at baseline. (supplementary table 1).

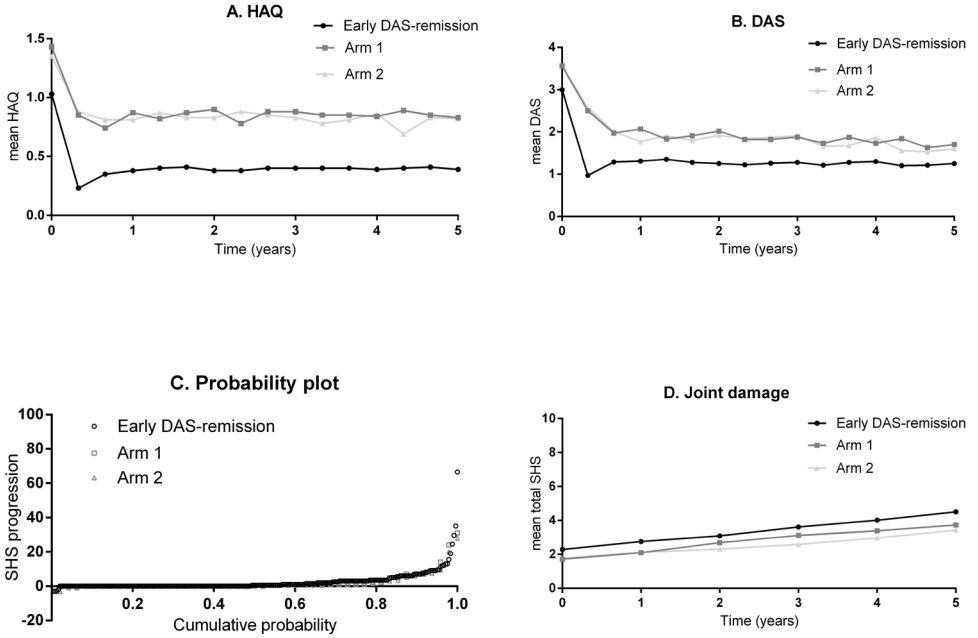


Figure 2A. HAQ over time, B. DAS over time, C. Probability plot after 5 years, D. total SHS over time after imputation.
A. Mean HAQ over time. B. mean DAS over time. C. Probability plot SHS progression in completers. D. mean total SHS over time after imputation.
HAQ: health assessment questionnaire; DAS: disease activity score; SHS: Sharp-van der Heijde score.

In general, patients who achieved early DAS-remission had better outcomes than patients in the randomisation arms or out of protocol group. Over five years, sustained drug-free remission was achieved by 135/387 (35%) in the early DAS-remission group, compared to 11% (9+10+5/83+78+50) in the other patients. At five years, 220/387 (57%) in the early DAS-remission group patients were in DAS-remission, and 111/387 (29%) in ACR/EULAR Boolean remission, compared to 75/211 (36%) and 26/211 (12%), respectively, in the other patients (supplementary table 1 and figure 3D). After imputation, radiologic damage progression

was similar in the early DAS-remission group and the other patients. Figure 2C shows the probability plot for SHS progression at five years, and figure 2D the mean total SHS after imputation at year five. More patients in the early DAS-remission group than the other patients had erosion progression.

In the early DAS-remission group use of medication initially decreased, then remained stable over time (figure 3A). In particular, the percentage of patients that were treated with prednisone dropped steeply, then remained low. MTX use also dropped and remained stable from year three. During five years 55/387 (14%) patients initially in early DAS-remission after DAS-increase were randomised in arm 1, of whom 30 later switched to adalimumab and 68 (17%) were randomised in arm 2. Up to 18% at five years switched to medication according to the rheumatologists' decision, of whom 38% used a biologic DMARD.

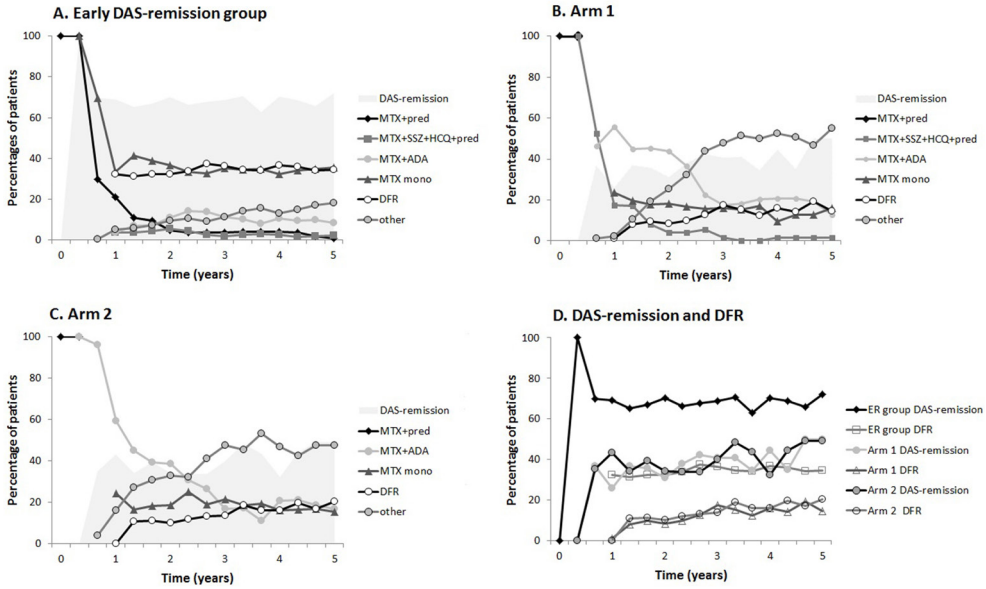


Figure 3: Treatment during 5 years in A. Early DAS-remission group, B. Arm 1, C. Arm 2, in percentage of completers per treatment group. D. Percentages in DAS-remission and percentages in drug-free remission per treatment group.

4A. Early DAS-remission group; 4B. Arm 1; 4C. Arm 2. Lines are approximations of the proportions of patients discontinuing medications (according to tapering strategies or due to side effects), or starting medications according to DAS-remission steered escalation strategies, across various treatment steps per arm, during 5 years. Percentages are calculated for completers per time point. The category 'Other' includes medications that were prescribed per protocol in the 'treatment according to rheumatologist' step after failure on methotrexate plus adalimumab, as well as medications prescribed outside of the protocol but still maintaining a DAS-remission targeted strategy. Shaded areas denote patient proportions in DAS-remission during five years.

4D. Proportions of patients in DAS-remission and drug-free DAS-remission per strategy over time.

Abbreviations: MTX: methotrexate; pred: prednisone; SSZ: sulphasalazine; HCQ: hydroxychloroquine; ADA: adalimumab; mono: monotherapy; DFR: drug-free (DAS-) remission; ER: Early DAS-remission.

Comparison between randomization arms

At five years, 31/83 (37%) in arm 1 and 29/78 (37%), p=0.768 in arm 2 were in DAS-remission, 9/83 (11%) in arm 1 and 12/78 (15%), p=0.374 in arm 2 were in drug-free remission (table 2), and 8/83 (10%) in arm 1 and 13/78 (17%), p=0.186 in arm 2 were in ACR/EULAR Boolean remission.[6] Over five years, sustained drug-free remission was achieved by 9/83 (11%) in arm 1 and 10/78 (13%) in arm 2, p=0.698. Mean (SD) HAQ improvement from baseline to five years was -0·6 (0·7) in arm 1 and -0.6 (0.8) in arm 2 (figure 2A), mean HAQ over time and mean DAS over time were the same in both arms (HAQ 0.9 (0.5), DAS 2.1 (0.6)) (figure 2A and 3B). At five years, 21/83 (25%) in arm 1 and 19/78 (24%) in arm 2 had a HAQ <0.5, approaching normal daily functioning. After five years, radiographs at baseline and five years were available in 362/610 patients (362/458 of patients still in the study after five years). After imputation, radiologic progression was similar in both arms (figure 2D).

Table 2: Outcomes at time of randomisation and after 5 years in the randomisation arms.

4 months	**Arm 1 n=83**	**Arm 2 n=78**	
DAS, mean ± SD	2.5 ± 0.6	2.6 ± 0.7	
HAQ, mean ± SD	0.9 ± 0.6	1.7 ± 0.7	
Swollen Joint Count, median (IQR)	1 (0-4)	2 (1-5)	
Tender Joint Count, median (IQR)	4 (3-7)	5 (3-9)	
ESR mm/hr, median (IQR)	13 (7-22)	11 (6-19)	
VAS global health (mm), mean ± SD	1.7 ± 0.7	1.7 ± 0.7	
5 years	**n = 62**	**n = 59**	**p-value**
DAS, mean ± SD	1.7 ± 0.7	1.6 ± 0.8	0.469
HAQ, mean ± SD	0.8 ± 0.7	0.8 ± 0.6	0.936
Swollen Joint Count, median (IQR)	0 (0-1)	0 (0-2)	0.200
Tender Joint Count, median (IQR)	1 (0-3)	1 (0-4)	0.818
ESR mm/hr, median (IQR)	11 (7-23)	12 (6-19)	0.517
VAS global health (mm), mean ± SD	31 ± 22	27 ± 23	0.369
Total SHS, median (IQR) (observed)	1 (0-4.9)	1.7 (0-4.1)	0.816
Total SHS, median (IQR) (after imputation)	1.3 (0.2-4)	1.9 (0-4)	0.340
Erosive, n (%) (observed)	13 (21)	13 (22)	0.828
Erosive, n (%) (after imputation)	19 (23)	16 (21)	0.753
SHS progression, median (IQR) (observed)	0 (0-1)	0 (0-1)	0.818
SHS progression, median (IQR) (after imputation)	0.5 (0-1.7)	0.3 (0-1.5)	0.115
SHS progression ≥0.5, n (%) (observed)	23 (37)	23 (39)	1.000
SHS progression ≥0.5, n (%) (after imputation)	46 (55)	37 (47)	0.327
SHS progression ≥5, n (%) (observed)	9 (15)	7 (12)	0.710
SHS progression ≥5, n (%) (after imputation)	11 (13)	9 (12)	0.653
SHS progression ≥10, n (%) (observed)	3 (5)	2 (3)	0.968
SHS progression ≥10, n (%) (after imputation)	4 (5)	2 (3)	0.712
In DAS-remission, n (%)	31 (50)	29 (49)	0.768
In drug-free remission, n (%)	9 (15)	12 (20)	0.374
In ACR/EULAR Boolean remission, n (%)	8 (13)	13 (22)	0.186

DAS: disease activity score; HAQ: health assessment questionnaire; ESR: erythrocyte sedimentation rate; VAS: visual analogue scale; SHS: Sharp-van der Heijde score; Erosive: ≥1 erosions; ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; n: number.

In arm 1 up to 75% (62/83) of patients over time switched to MTX+adalimumab because DAS-remission was not (re)achieved, and of these, 66% had increased adalimumab to 40mg/week. Treatment with adalimumab decreased to 13% of initial users at five years (figure 3B), either after successful tapering, or because DAS-remission was not achieved. At five years, 55% of patients use 'other medication', in 41% of cases another biologic DMARD.
In arm 2, 45/78 (58%) of patients who started on adalimumab increased the dose to once weekly. At five years, 17% of patients still/again used adalimumab, and 48% of patients had proceeded to 'other medication', in 39% of cases another biologic DMARD (figure 3C).
During five years of follow-up 95% in arm 1 and 96% in arm 2 had at least one adverse event, 22 per 100 patient years per arm. Serious adverse events occurred in 5.3 per 100 patient years in arm 1 and 7.6 per 100 patients years in arm 2 (p=0.140) (supplementary table 2). Two patients in arm 1 died (1 of haemorrhagic cerebrovascular accident and 1 of metastatic pancreatic carcinoma), 4 in arm 2 (1 of cerebral tumour, 1 of pneumococcal sepsis, 1 of pulmonary embolism and 1 of colon carcinoma).

Other comparisons between patients

At five years, 234/479 RA patients (49%) and 61/131 (47%), p=0.366 UA patients were in DAS-remission. More UA (41/131 (31%)) than RA patients (93/479 (19%), p<0.001 were in drug-free remission at five years. Over five years, sustained drug-free remission was achieved by more UA patients 49/131 (37%) than RA patients 110/479 (23%), p=0.001. These results in part overlap with the findings that at five years more RF-negative patients (69/245, 28%) than RF-positive patients (58/339, 17%, p<0.001), and more ACPA-negative (81/262, 31%) than ACPA-positive patients (50/332, 15%, p<0.001) were in drug-free remission. However DAS-remission rates were similar in RF-positive and RF-negative patients (171/339 (50%) versus 111/245 (45%), p=0.611) and in ACPA-positive and ACPA-negative patients (172/332 (52%) versus 120/262 (46%), p=0.887). DAS-remission rates and drug-free remission rates at five years were similar in anti-CarP-positive and anti-CarP-negative patients (88/172 (51%) vs 163/350 (47%), p=0.374 for DAS-remission and 33/172 (19%) vs 82/350 (23%), p=0.139 for drug-free remission). Over five years, sustained drug-free remission was achieved by more RF negative patients 79/245 (32%) compared to RF positive 74/339 (22%), p=0.005. Sustained drug-free remission was also achieved by more ACPA negative patients 96/262 (37%) than ACPA positive patients 60/332 (18%), p<0.001. Also, more anti-CarP negative patients (106/350 (30%)) were in sustained drug-free remission over time compared to anti-CarP positive patients (35/172 (20%), p=0.016). Mean DAS and HAQ over time were similar in autoantibody (RF, ACPA and anti-CarP) positive and negative patients. Only HAQ over time was significantly different between anti-CarP positive (0.6 (0.5)) and anti-CarP negative (0.7 (0.5), p=0.031) patients. Mean HAQ over time was similar in RA and UA patients and mean DAS over time was significantly lower in UA patients 1.5 (0.6) compared to RA patients

1.7 (0.7), p=0.003. DAS-remission rates at five years were similar in patients with baseline symptom duration <12 weeks (95/204, 47%) or ≥12 weeks (196/397, 49%) (p=0.740), and 51/204 (25%) of patients with symptom duration<12 weeks were in drug-free remission compared to 82/397 (21%) of patients with symptom duration ≥12 weeks (p=0.071).
More ACPA positive patients compared to ACPA negative patients had SHS progression (193/333 (58%) ≥0.5 SHS after 5 years versus 117/255 (46%), p<0.001, 54/333 (16%) ≥5 SHS versus 22/255 (9%), p<0.001), with a higher median progression score (0.8 (0-3) versus 0.3 (0-1.8), p<0.001). Also erosive disease was seen in more ACPA positive patients (119/333 (36%, was 17% at baseline)) than in ACPA negative patients (41/255 (16%, was 9% at baseline), p<0.001 for comparison at five years). More RA than UA patients had SHS progression (257/479 (54%) versus 60/131 (46%), p<0.001) with a higher median (0.5 (0-3) versus 0.4 (0-1.9), p=0.024).

DISCUSSION

This study shows for the first time that sustained (≥1 year) drug-free remission can be achieved in about a quarter of early rheumatoid or undifferentiated arthritis patients. Irrespective of DMARD use, after five years 48% of patients were in DAS-remission. Functional ability approached normality in these patients, and radiologic damage progression was generally well suppressed. In the whole cohort, UA patients, overlapping with patients who were negative for autoantibodies, achieved more drug-free remission than RA patients and autoantibody positive patients, but overall showed similar disease activity and functional ability over time, and similarly little radiologic damage progression. In general, patients who were in DAS-remission after four months treatment had better outcomes than patients who were not, despite continuous drug-free remission steered treatment adjustments in all patients. We found no differences in outcomes between two treatment strategy arms in the patients who did not achieve early DAS-remission on the initial treatment of methotrexate and a tapered high dose of prednisone. Initially, as reported earlier, patients randomised to switch immediately to adalimumab achieved more DAS-remission at year one than patients who first expanded the initial treatment with other synthetic antirheumatic medications.[7] However, after five years there are no lasting clinical nor radiological benefits, with reasonably good functional ability and little damage progression in both arms. Toxicity over time was similar and generally as expected.
Our study shows that MTX with a tapered high dose of prednisone is effective as DAS-remission induction therapy in 63% of patients and that these patients continue to have better outcomes during long term follow-up compared to patients who do not achieve early DAS-remission. These patients already had lower DAS and HAQ at baseline, placing the DAS-

target within closer reach. In previous cohorts, presence of ACPA was associated with worse outcomes in patients with UA and RA.[18, 19] A previous sub-analysis in the current IMPROVED-study showed that presence of ACPA, baseline DAS, HAQ, symptom duration, male gender and BMI were associated with achieving early DAS-remission.[13] After one year, presence or absence of ACPA was not associated with achieving drug-free remission in the early DAS-remission group.[7] However, in the next four months, ACPA positive patients were more at risk than ACPA negative patients to lose drug-free remission, having to restart medication,[20] a trend which is now confirmed with finding fewer ACPA positive patients than ACPA negative patients achieving sustained drug-free remission. In addition, absence of autoantibodies and not fulfilling the ACR/EULAR 2010 classification criteria for RA (which rest heavily on the presence of ACPA) were associated with being in drug-free remission after five years. Total damage progression after five years was similar in patients who were or were not in early DAS-remission, but we saw slightly more erosive joint damage progression in patients in the early DAS-remission group. It may be that due to more drug tapering to drug-free remission, and less use of anti-TNF therapy compared to the other treatment groups, there may have been subclinical inflammation. On the other hand, more patients in the early DAS-remission group already had erosions at baseline, which is associated with more erosion progression.[21] Previous studies aiming at low DAS (≤2.4)[22, 23] or even stricter remission definitions than DAS-remission,[24, 25] despite reporting similar or higher remission rates, reported more radiological damage progression than in our study, possibly due to inclusion of patients with more severe and/or advanced disease. Compared to the other studies, radiologic damage progression may even be relatively overestimated, as we scored subsequent radiographs in chronologic order, whereas in the other studies the time order was random. The used scoring method is aimed to detect small changes, which may have limited clinical relevance. We reported progression <0.5 points as absolute negative of 'no progression', and >5 points as positive, as this was considered by experts to be clinically relevant, albeit *per year*,[15] which would expand to 25 points during the course of this study. Only five of our patients had progression >25 points.

This study is the first to aim for relatively rapid tapering of medication aiming at sustained drug-free remission, which we felt is the outcome closest approaching cure. Therefore we aimed to include and treat patients in an early phase of RA (even if classification criteria were not yet met), as it appears that earlier treatment may result in better and long-lasting suppression of inflammatory processes, which at that time may be reversible. During this so-called 'window of opportunity', estimated to encompass around 12 weeks from symptom onset,[12] chronicity of inflammation may be prevented and potentially prolonged remission may be induced.[26-28] However, we found few differences in DAS-remission rates and only a trend for more drug-free remission in patients with symptom duration <12 weeks compared to ≥12 weeks. As this time window is based on studies with slow acting DMARDs, thanks to drug tapering strategies the use of prednisone over time was low. Also, in the early DAS-remission

group, use of adalimumab and other biologic DMARDs (as option in case of failure to achieve DAS-remission on adalimumab) was low. Most patients were on MTX monotherapy or in drug-free remission. In the randomisation arms, use of adalimumab stabilized at twice the level of use as in the early DAS-remission group and also use of other biologic DMARDs was higher, which implies that treatment costs in both arms were higher than in the early DAS-remission group. Toxicity in the early DAS-remission group and the randomisation arms was roughly comparable.

There are several limitations to the study design. First, we cannot claim that the good clinical and radiologic outcomes are the result of the initial treatment, subsequent medications, or the DAS-remission steered treatment adjustments, as there is no arm in which we did not adapt the treatment strategy to induce early remission, nor did we include an arm where a spontaneously disease course could be observed. We may have temporarily over-treated patients who would have achieved spontaneous remission. This was part of the reason why we chose to taper and discontinue medication early. We chose the MTX and prednisone doses for induction therapy based on the results of the COBRA[29] and BeSt-study. More recent studies[30, 31] have shown that lower dosages of prednisone may be equally effective. The four-monthly evaluation time points may not have provided sufficiently tight control in combination with targeted treatment. This, together with more rapid tapering strategies than were previously introduced in the BeSt-study, may have resulted in fewer patients achieving sustained (drug-free) DAS-remission than we hoped. Our treatment target of DAS-remission may be insufficiently stringent, even though we used the original DAS and not the DAS28 which is based on the evaluation of fewer joints. More patients might have achieved drug-free remission if we had aimed at a more strict remission definition, but also it would have risked higher use of costly medications in patients who would not achieve this threshold. All definitions of remission may be influenced by non-inflammatory pain.[32] Finally, early study termination in the various patient groups may have influenced the results.

In conclusion, after five years of DAS-remission steered treatment, 48% of early RA and UA patients were in DAS-remission and 26% in sustained in drug-free remission. HAQ results indicate almost normal functional ability over time and radiological damage progression was generally well suppressed in all groups. Patients with milder disease activity at baseline who achieve more often early DAS-remission continue to do better than other patients while using less antirheumatic medication. Most results were similar for RA and UA patients, autoantibody positive or negative patients, but more UA patients and autoantibody negative patients achieved drug-free remission at five years. If DAS-remission is not achieved after four months, immediate introduction of adalimumab has limited benefits over first expanding treatment with synthetic DMARDs.

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SUPPLEMENTARY FILE

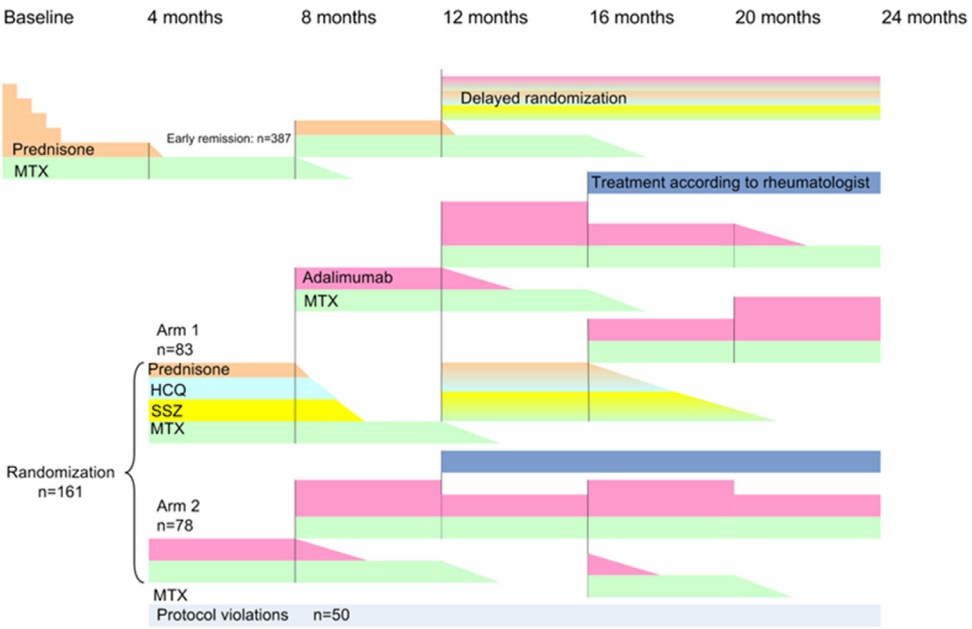


Figure S1: Study flow chart IMPROVED-study
DFR: drug-free DAS-remission, MTX: methotrexate, HCQ: hydroxychloroquine, SSZ: sulphasalazine. Colours: orange=prednisone, green=MTX, dark blue=treatment according to opinion rheumatologist (TAR), aqua=HCQ, yellow=SSZ, purple=adalimumab biweekly, double thickness purple=adalimumab weekly, grey=protocol not followed as required but remained in follow up (outside of protocol, OP).

Table S1: (Serious) adverse events per 100 patient years during 5 years according to the different treatment groups.

	Total population	Early DAS-remission	No early DAS-remission		
	n=610	n=387	Arm 1 n=83	Arm 2 n=78	OP n= 50
AE per 100 patient years	21.4	20.8	22.2	22.0	24.3
Type of AE					
Cardiovascular	4.5	4.0	4.5	6.8	5.0
Pulmonary	3.1	3.0	3.4	2.4	4.4
Gastrointestinal	11.2	10.8	11.5	13.2	9.9
Neuropsychiatric	6.4	6.0	8.2	6.8	6.6
Metabolic	1.5	1.3	1.4	2.7	1.7
Hematological	0.8	0.8	1.4	0.9	-
Urogenital	1.8	1.9	1.7	1.8	1.1
Skin/mucous membranes	8.3	8.3	8.2	7.9	9.4
Infections	12.9	12.4	11.8	15.9	14.9
Auto-immune	0.2	0.1	0.6	-	-
Malignancy	0.4	0.3	0.3	0.9	0.6
Trauma/injury	3.2	3.1	3.7	2.4	4.4
Infusion reaction	0.3	0.2	0.6	0.3	-
Malaise	2.5	2.3	3.9	2.4	1.7
Surgical procedures without hospitalization	2.7	2.4	3.4	3.5	2.8
Other	9.6	8.8	12.9	10.0	10.5
SAE per 100 patient years	5.7#	4.9	5.3	7.6	8.3
Hospital admissions per 100 patient years	4.8#	4.2	4.5	7.1	6.1
Malignancies, n	39#	25	4	6	3
Deaths, n	17#	8	2	4	1
Causes of death	1 infection, 1 CVD#	4 malignancies, 4 CVD	1 malignancy, 1 CVD	2 malignancies, 1 infections, 1 CVD	1 malignancy

OP: outside of protocol, AE: adverse event, SAE: serious adverse event, CVD: cardiovascular disease; n: number; # 4 patients had SAE's after baseline and left the study before the assessment at 4 months.

Table S2: Baseline characteristics and 4 month outcomes of patients who did or did not achieve early DAS-remission.

	Early DAS-remission	No early DAS-remission
Baseline	**n = 387**	**n = 211**
DAS, mean ± SD	3·0 ± 0·8	3·6 ± 0·9
HAQ, mean ± SD	1·0 ± 0·7	1·4 ± 0·6
Age in years, mean ± SD	52 ± 14	51 ± 14
Female, n (%)	240 (62)	164 (78)
Symptom duration (weeks), median (IQR)	17 (9-30)	21 (9-38)
RF positive, n (%)	224 (58)	107 (51)
ACPA positive, n (%)	225 (58)	102 (48)
Anti-CarP positive, n (%)	118 (30)	51 (24)
Fulfilled RA(2010) classification criteria, n (%)	298 (77)	172 (82)
Swollen Joint Count, median (IQR)	5 (2-9)	7 (3-12)
Tender Joint Count, median (IQR)	5 (3-8)	9 (6-13)
ESR mm/hr, median (IQR)	23 (8-38)	26 (13-41)
VAS global health (mm), mean ± SD	43 ± 24	52 ± 21
Total SHS, median (IQR) (observed)	0·5 (0-3)	0 (0-2·5)
Total SHS, median (IQR) (after imputation)	0·5 (0-3)	0 (0-2·9)
Erosive, n (%) (observed)	55 (14)	18 (9)
Erosive, n (%) (after imputation)	59 (15)	20 (9)
4 months		
DAS, mean ± SD	1·0 ± 0·4	2·5 ± 0·7
HAQ, mean ± SD	0·2 ± 0·3	0·8 ± 0·6
Swollen Joint Count, median (IQR)	0 (0-0)	1 (0-4)
Tender Joint Count, median (IQR)	0 (0-1)	5 (3-8)
ESR mm/hr, median (IQR)	6 (3-12)	12 (6-22)
VAS global health (mm), mean + SD	14 ± 14	36 ± 21

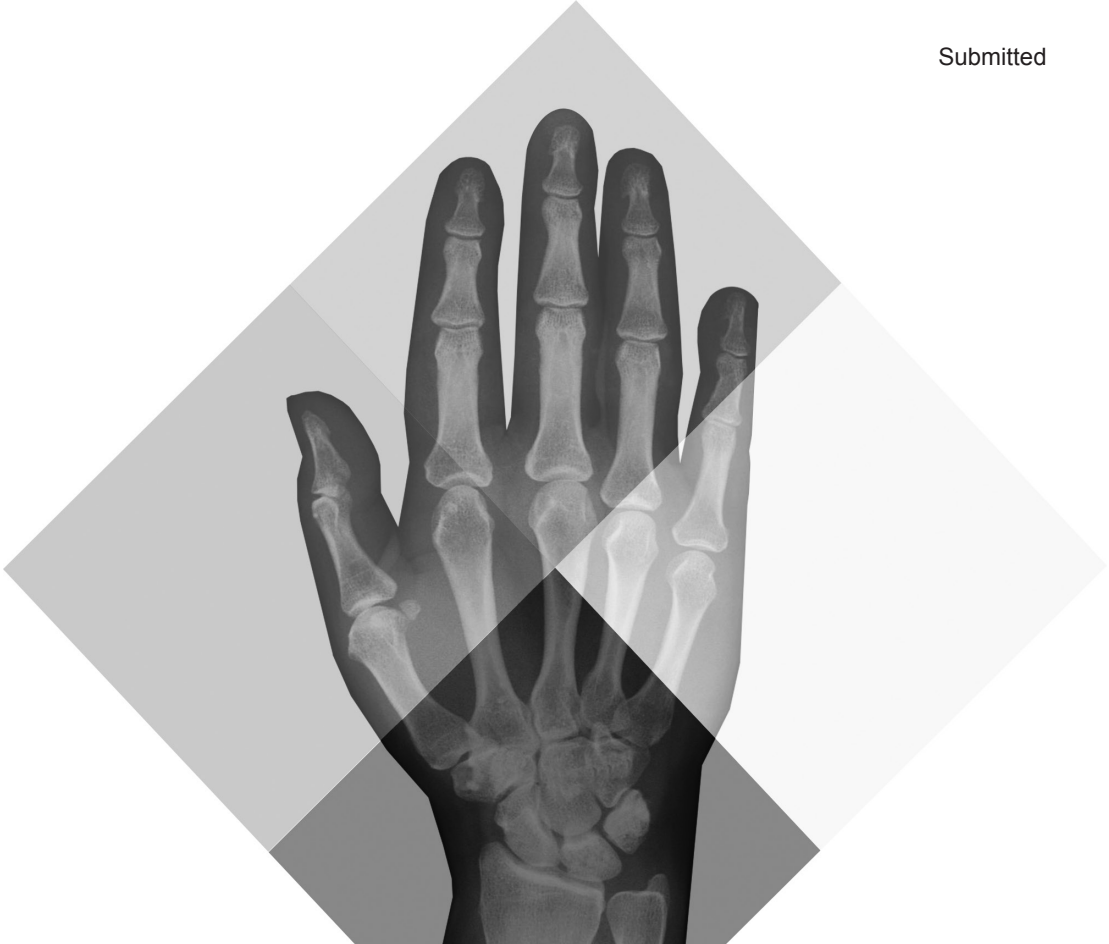
DAS: disease activity score; HAQ: health assessment questionnaire; RF: rheumatoid factor; ACPA: anti-citrullinated protein antibodies; RA: rheumatoid arthritis; Anti-CarP: anti-carbamylated protein antibodies; ESR: erythrocyte sedimentation rate; VAS: visual analogue scale; SHS: Sharp-van der Heijde score; Erosive: ≥1 erosions; n: number.

Chapter 5

SIGNS OF INFLAMMATION ON MAGNETIC RESONANCE IMAGING BEFORE AND AFTER INTRA-ARTICULAR INFLIXIMAB OR CORTICOSTEROIDS IN RECURRENT GONARTHRITIS

Gülşah Akdemir, Arie E. van der Bijl, Badelog J.E. de Lange-Brokaar,
Tom W.J. Huizinga, Cornelia F. Allaart, Margreet Kloppenburg

Submitted



ABSTRACT

Objectives

To evaluate synovial inflammation on magnetic resonance (MR) imaging in chronic or recurrent gonarthritis and changes after intra-articular (i.a.) infliximab (IFX) or methylprednisolone (MP) treatment in relation to clinical response.

Methods

In the RIA study, a prospective double-blind trial, chronic or recurrent gonarthritis patients were randomized to i.a. IFX or MP. Changes in T1 contrast enhanced MR outcomes of the knee pre-injection and 4 weeks post-injection were compared for Hoffa synovitis (0-3) and joint effusion (0-3), and investigated in relation to early clinical response measured by the knee joint score (tenderness, swelling, patient's pain) after 4 weeks and late clinical response measured by relapse within 6 months.

Results

Sets of pre- and post-injection MR images were available for 26 injections (14 IFX, 12 MP) in 20 knees. Pre-injection, MR findings were not associated with patient or gonarthritis characteristics. Hoffa synovitis and effusion decreased in IFX injected knees ((2.5 (1.8;3.0) to 2.0 (1.0;2.3), p=0.021) (2.5 (2.0;3.0) to 1.0 (1.0;3.0), p=0.007), respectively). In IFX injected knees, but not in MP injected knees, MR improvement after 4 weeks was associated with clinical improvement. Relapse within 6 months occurred in all IFX and in half of MP injected knees, irrespective of MR or early clinical improvement at 4 weeks.

Conclusions

MR of chronic or recurrent gonarthritis, showed considerable signs of inflammation. IFX injected knees showed early clinical and MR improvement, this was not seen in MP injected knees. However at the long term MP injected knees showed less relapse than IFX injected knees.

INTRODUCTION

Isolated gonarthritis in daily practice is mostly treated with local corticosteroid injections, but this treatment is associated with a high recurrence rate.[1] An alternative treatment with intra-articular (i.a.) injections of infliximab (IFX), a tumour necrosis factor α blocker, has been tried in several studies.[2-5] These showed promising clinical responses, but were uncontrolled, open label and with relatively short follow up. To evaluate whether i.a. infliximab was superior to (retreatment with) i.a. corticosteroids in chronic gonarthritis that had persisted or recurred after previous i.a. corticosteroid treatment, we conducted the RIA study, a double-blind randomized controlled trial in patients with chronic gonarthritis to compare the 6 months clinical outcomes of i.a. infliximab and i.a. methylprednisolone (MP).[6] The results were disappointing: 100% of IFX injected knees showed persistence or recurrence of gonarthritis after 6 months, compared to 50% of MP injected knees.

We hypothesized that either the pre-treatment amount of inflammation was too high to (permanently) improve after local injection, or that initial improvement may have occurred but untreated disease mechanisms have resulted in recurrence of inflammation. To investigate this hypothesis, we assessed pre- and 4-weeks post-injection magnetic resonance (MR) imaging of the treated knees. MR imaging enables the evaluation of soft tissues as well as of bone in joints. Earlier studies showed that MR signs correlate well with histological findings of inflamed synovium [7,8] and that these signs may improve early after i.a. corticosteroid injection.[9] Here we report pre-injection inflammatory MR signs and their improvement after treatment with either i.a. IFX or MP injections in relation to clinical response in patients with chronic or recurrent gonarthritis.

PATIENTS AND METHODS

Study design and Patients

The RIA study (Remicade Intra Articularly), a prospective, randomized, double-blind trial, included 23 patients from the outpatient clinic of the Rheumatology department of the Leiden University Medical Center. These patients had clinically active monoarthritis of the knee and had been treated with i.a. corticosteroid injection at least once in the previous year. Exclusion criteria were gonarthritis caused by an infection, gout or osteoarthritis, hemorrhagic disease, participation in any other study that could be influenced by this study, use of oral prednisone >10 mg/day, change of disease modifying antirheumatic drug (DMARD) therapy ≤6 weeks before inclusion, i.a. injection with corticosteroid in any joint <2 months, hypersensitivity to methylprednisolone, lidocaine, or infliximab (or other murine proteins), active or latent tuberculosis, acute or chronic infection, multiple sclerosis, heart failure, pregnancy or lactation,

and malignancy. All patients were screened for (latent) tuberculosis including radiograph of the lungs and a tuberculin skin test. The study was approved by the hospital's Medical Ethics Committee and all patients gave written informed consent.
Patients were randomized to receive i.a. infliximab 100 mg or i.a. corticosteroid 80 mg in the knee. If gonarthritis recurred clinically within 3 months patients could receive a second injection with the other study medication in the same knee.
Study medication was prepared by a 'non-assessing' investigator who made sure that patient, rheumatologist and assessor remained blind for the injected medication. Prior to injection of the study medication, i.a. fluid was evacuated by aspiration as much as possible.

Outcomes
All patients were clinically evaluated at 4 weeks, 3 and 6 months. Outcome measures were event-free survival and/or non-improvement of the knee joint score. This arbitrary score (0-7) includes knee tenderness 0-3 (0 = no tenderness, 1 = tenderness when asked, 2 = tenderness on pressure and 3 = tenderness and wincing), knee swelling 0-3 (0 = no swelling, 1 = little swelling, 2 = moderate swelling and 3 = abundant swelling) and a patient's knee pain score 0-1 (visual analogue scale, VAS, measured in mm, 0=best possible, 100=worst possible, divided by 100). Event free survival was defined by time from i.a. treatment until local retreatment (joint aspiration or injection, arthroscopy, or (radio-) synovectomy) was performed due to recurrence or persistency of the gonarthritis (which will be referred to as 'relapse').

MR and scoring
A T1 gadolinium contrast enhanced MR (CE-MR) of the affected knee was performed at baseline preceding the i.a. injection and 4 weeks later. A 3 T Philips Achieva MR system (Philips Healthcare) using an eight-channel dedicated knee coil was used. In case of recurrent or persistent gonarthritis, patients entered the cross-over part of the study and CE-MR was again performed prior to and 4 weeks after the second injection. Per patient a decision was made to withhold gadolinium (8 pre-treatment MRs and 7 post-treatment MRs). The Guermazi score was therefore dropped from the analysis.
All MR images were scored by one trained reader. Since there is no validated scoring method to assess (changes in) MR signs in inflammatory gonarthritis, the MR images were assessed by 3 scoring methods more specific for osteoarthritis. Sagittal T2 proton density weighted images were used for the MOAKS [10] (MR Osteoarthritis Knee Score) was used to assess Hoffa synovitis (range 0-3, 0 = no synovitis, 1 = mild synovitis, 2 = moderate synovitis and 3 = severe synovitis). Axial and coronal T2 proton density weighted images were used for the KOSS [11] (Knee Osteoarthritis Scoring System) to assess joint effusion (range 0-3, 0 = no effusion, 1 = mild effusion, 2 = moderate effusion, 3 = severe effusion). Sagittal T1 CE-MR images were used for the Guermazi [12] scoring method to assess synovitis on 8 anatomical

sites in the knee: suprapatellar, infrapatellar, intercondylar, adjacent to the anterior cruciate ligament (ACL), parameniscal lateral, parameniscal medial, adjacent to the posterior cruciate ligament (PCL) (per anatomical site range 0-2 (0 = synovial thickness less than 2 mm, 1 = thickness between 2 and 4 mm, 2 = thickness above 4 mm) and if loose bodies were present, this site was scored in addition. A total score was calculated (0-16). Intra-observer reliability was measured by intraclass correlation coefficient (ICC) and ranged from a minimal value of 0.70 for the Hoffa synovitis score to a maximal value of 0.94 for the effusion score.

Statistical analysis

Differences between two consecutive MR images were compared between the randomization groups using Mann-Whitney *U* test, Wilcoxon signed ranks test and χ^2 test. As there was no statistical significant difference in the primary clinical endpoint (knee joint score) between the randomization arms, and no differences in MR scores pre-injection between once or twice injected knees between the randomization arms, we assumed no cross-over or carry over effects of treatments, and analyzed all interventions together. Statistical analysis were performed by SPSS 23.0.

RESULTS

MR images preceding injection

In the RIA study, 23 middle-aged, majority male patients, 35% were diagnosed with UA, were included, who in total received 41 i.a. knee injections: 15 single injections, 13 same-knee re-injections. Pre- and post-injection MR images were unfortunately not complete, due to patients' refusal, contra-indications to gadolinium, or rescheduling of MR appointments resulting in inadequate timing respective to the injections. In 21 patients MR images preceding 1st, 2nd or 3rd injections were obtained (table 1). At baseline (preceding the first injection) 18 MR images (4 had no post-injection MR images) were available, 12 MR images preceding the second injection (2 had no post-injection MR images) and 2 preceding the third injection.
Evident signs of inflammation of the knee were seen by a median knee joint score at inclusion of 3.7 (table 1). Median Hoffa synovitis score was 2 and effusion score was 3. Guermazi scores were missing in 9 patients, because these patients did not receive gadolinium. Median Guermazi synovitis total score was 7. The medians for the 8 different anatomical sites were approximately 1 (supplementary table 1) and only the score for 'loose body' was 0.
MR scores were comparable in knees with various diagnoses (data not shown).
Preceding the first injection, there were no differences in MR scores between MP and IFX injected knees (Hoffa synovitis score mean difference -0.69 (95% CI -1.44;0.05) and effusion score 0.31 (-0.33;0.95)), or in knees injected once or twice (in cross-over design) with study medication (data not shown).

Table 1. Baseline patient characteristics and MR signs on images preceding injections (n=32 interventions in 21 patients).

MR preceding 1st, 2nd or 3rd injection	Patients n=21
Age, years, mean (SD)	51 (12)
Female, n (%)	10 (48)
Diagnosis, n (%)	
UA	9 (42.9)
RA	4 (19)
PsA	5 (23.8)
SpA	2 (9.5)
JIA	1 (4.8)
Number of DMARDs, median (IQR)	1 (0;2)
Number of previous i.a. corticosteroid injections, median (IQR)	2 (1;3)
	Interventions n=32
Randomization MP/IFX, n (%)	15/17 (47/53)
Knee joint score at time of inclusion (0-7), median (IQR)	3.7 (3.3;4.8)
Knee tenderness (0-3), median (IQR)	1 (0.8;2)
Knee swelling (0-3), median (IQR)	2 (2;3)
Patient knee pain score (0-1), median (IQR)	0.40 (0.20;0.64)
Hoffa synovitis, n (%)	
Mild	6 (19)
Moderate	13 (41)
Severe	11 (34)
Effusion, n (%)	
Mild	3 (9)
Moderate	9 (28)
Severe	18 (56)
Guermazi score, median (IQR)	7 (5.8;10.3)

UA: undifferentiated arthritis; RA: rheumatoid arthritis; PsA: psoriatic arthritis; SpA: spondyloarthritis; JIA: juvenile idiopathic arthritis; DMARDs: disease modifying antirheumatic drugs; i.a.: intra-articular; IFX: infliximab; MP: methylprednisolone; VAS: visual analogue scale; SD: standard deviation; n: number; IQR: interquartile range.

Changes in MR scores

There were 26 sets of pre- and post-injection MR images. These comprised 14 sets around first injections (6 MP, 8 IFX), 10 sets around second injections (5 MP, 5 IFX), 8 in a previously injected knee, and 2 sets around third injections (1 with MP in a previously injected knee and 1 with IFX in the contralateral knee), thus making 12 sets of knee MR images pre-injection and post-injection with MP, and 14 sets of knee MR images pre-injection and post-injection with IFX. A second injection in the contralateral knee will further be considered to be a first injection in that knee. Thus there were 17 first injections (7 MP, 10 IFX) and 9 second injections (5 MP, 4 IFX). All 26 sets were combined in one analysis, although details about retreated knees will be presented.

There were no differences between IFX injected patients and MP injected patients in age, number of DMARDs, number of previous i.a. corticosteroid injections, distribution of diagnoses nor between injected knees in knee joint scores at the time of inclusion (table 2).

Table 2. Clinical characteristics of patients at inclusion classified per injection (n=26 injections).

	Total patients n=18	**MP n=10**	**IFX n=14**
Age, years, mean (SD)	51 (13)	51 (13)	50 (13)
Female, n (%)	8 (44)	2 (20)	7 (50)
Diagnosis, n (%)			
UA	6 (33)	2 (20)	4 (29)
RA	4 (22)	2 (20)	3 (21)
PsA	5 (28)	4 (40)	4 (29)
SpA	2 (11)	1 (10)	2 (14)
JIA	1 (6)	1 (10)	1 (14)
Number of DMARDs, median (IQR)	1 (0;2.3)	0.5 (0;2.3)	1 (0;2.3)
Number of previous i.a. corticosteroid injections, median (IQR)	2 (1;3)	2.5 (1;11.3)	2 (1;2.3)
	Total interventions n=26	**MP n=12**	**IFX n=14**
Knee joint score at time of inclusion (0-7), median (IQR)	3.7 (3.3;5)	3.7 (3.3;5)	3.6 (3.1;5)
Knee tenderness (0-3), median (IQR)	1 (0.3;2)	1 (1;2)	1 (0;2)
Knee swelling (0-3), median (IQR)	2 (2;3)	2 (2;3)	2 (2;3)
Patient knee pain score (0-1), median (IQR)	0.37 (0.20;0.67)	0.39 (0.32;0.58)	0.36 (0.13;0.74)
Hoffa synovitis, n (%)			
Mild	5 (19)	2 (17)	3 (21)
Moderate	11 (42)	7 (58)	4 (29)
Severe	9 (35)	2 (17)	7 (50)
Effusion, n (%)			
Mild	3 (12)	1 (8)	2 (14)
Moderate	7 (27)	2 (17)	5 (36)
Severe	15 (58)	8 (67)	7 (50)
Guermazi score, median (IQR)	8 (6;10.5)	6 (5;8)	9 (6.3;11)

IFX: infliximab; MP: methylprednisolone; UA: undifferentiated arthritis; RA: rheumatoid arthritis; PsA: psoriatic arthritis; SpA: spondyloarthritis; JIA: juvenile idiopathic arthritis; DMARDs: disease modifying antirheumatic drugs; i.a.: intra-articular; VAS: visual analogue scale; MOAKS: MR Osteoarthritis Knee Score; KOSS: Knee Osteoarthritis Scoring System; SD: standard deviation; n: number; IQR: interquartile range.

First we looked at changes in MR outcomes 4 weeks post-injection in relation to treatment. Following injection the Hoffa synovitis score improved by ≥1 point in 12/26 (46%) knees (4/12 (33%) MP injected knees and 8/14 (57%) IFX injected knees, p=0.302), while synovitis score remained stable in 13/26 (50%) knees (7/12 (58%) MP injected knees and 6/14 (43%) IFX

injected knees, p=0.302, incomplete data for 1 MP injected knee). Following injection, the effusion score improved by ≥1 point in 11/26 (42%) knees (3/12 (25%) MP injected knees and 8/14 (57%) IFX injected knees, p=0.227), while it remained stable in 14/26 (54%) knees (8/12 (67%) MP injected knees and 6/14 (43%) IFX injected knees, p=0.227, incomplete data in 1 MP injected knee). Irrespective of intra-articular medication, of 14 knees that showed improvement in Hoffa synovitis score or improvement in effusion score 9 showed improvement in both scores. In IFX injected knees, the mean decrease in Hoffa synovitis scores and effusion scores reached statistical significance (from 2.5 (1.8;3) to 2 (1;2.3), p=0.021 and from 2.5 (2;3) to 1 (1;3), p=0.007, respectively) but not in MP injected knees (from 2 (2;2) to 1.5 (1;2), p=0.157 and from 3 (2;3) to 2 (1;3), p=0.102, respectively) (table 3).

Second we looked at post injection MR outcomes in relation to early clinical response. Four weeks post injection, the knee joint score had improved by ≥1 point in 13/26 (50%) injected knees (6/12 (50%) MP injected knees and 7/14 (50%) IFX injected knees, p=1.000) with a median improvement from 3.7 (3.3;5) to 1.9 (0.8;3.6) in MP injected knees (p=0.012) and from 3.6 (3.1;5) to 1.7 (1;3.5) in IFX injected knees (p=0.038) (table 4). Early knee joint score improvement was associated with MR improvement only in IFX injected knees, where all knees with MR improvement also showed early clinical improvement. In MP injected knees, clinical improvement was seen more often in knees where no MR improvement was seen (table 4).

Six of twelve MP injected knees and all 14 IFX injected knees were defined as having a relapse 6 months after injection (p=0.04). MR changes nor early clinical improvement were related to clinical outcomes at 6 months (table 4). Median (IQR) Hoffa synovitis scores and effusion scores before injection were similar in MP injected knees that did or did not relapse (data not shown). Also the post-injection changes in Hoffa synovitis scores and effusion scores were similar (delta Hoffa synovitis scores 0 (-1.5;0.5) p=0.414 in MP injected knees with relapse and 0 (-1;0) p=0.157, in MP injected knees that did not relapse, delta effusion scores 0 (-1;0), p=0.157 in knees with relapse and 0 (-0.5;0) p=0.317, in knees without relapse). Knee joint score 4 weeks post-injection had decreased significantly in patients who had no relapse at 6 months (from 3.5 (3.4;4.7) to 1.1 (0.2;2.6), p=0.028) but less so in patients who did relapse (from 4.1 (3;5.4) to 3.9 (1.6;5.4), p=0.180) (table 5). These limited findings may suggest that there may have been a short term suppression of synovitis, but chronic inflammation then recurs.

Table 3. Clinical and MR outcomes before and 4 weeks after treatment and clinical outcome 6 months after treatment in the randomization groups.

Time point	MP n=12	p-value week 0 vs. 4 MP	IFX n=14	p-value week 0 vs. 4 IFX	p-value between MP and IFX
Total Knee joint score, median (IQR)					
Baseline	3.7 (3.3;5)		3.6 (3.1;5)		0.671
Week 4	1.9 (0.8;3.6)		1.7 (1;3.5)		1.000
Delta	-1 (-3.5;-0.8)	0.012	-1.6 (-3.1;0.03)	0.038	
Knee tenderness, median (IQR)					
Baseline	1 (1;2)		1 (0;2)		0.977
Week 4	1 (0;2.8)		0.5 (0;2)		0.582
Delta	0 (-1;0.3)	0.317	-0.5 (-1.3;0.3)	0.161	
Knee swelling, median (IQR)					
Baseline	2 (2;3)		2 (2;3)		0.755
Week 4	1 (1;2.8)		1 (1;2)		1.000
Delta	-1 (-2;-0.8)	0.009	-1 (-1.5;0)	0.014	
Patient knee pain score, median (IQR)					
Baseline	0.39 (0.32;0.58)		0.36 (0.13;0.74)		0.630
Week 4	0.31 (0.04;0.64)		0.26 (0.11;0.47)		0.923
Delta	-0.07 (-0.31;-0.02)	0.012	-0.06 (-0.38;0.04)	0.097	
Hoffa synovitis score, median (IQR)					
Baseline	2 (2;2)		2.5 (1.8;3)		0.288
Week 4	1.5 (1;2)		2 (1;2.3)		0.826
Delta	0 (-1;0)	0.157	-1 (-1.0)	0.021	
Effusion score, median (IQR)					
Baseline	3 (2;3)		2.5 (2;3)		0.286
Week 4	2 (1.3;3)		1 (1;3)		0.186
Delta	0 (-1;0)	0.102	-1 (-1;0)	0.007	
6 months					
Sufficient response*, n (%)	6 (50)		0		
Insufficient response, n (%)	6 (50)		14 (100)		0.004

IFX: infliximab; MP: methylprednisolone; n: number; IQR: interquartile range.
*no relapse before 6 months requiring therapeutic intervention

Of 9 patients who had a gonarthritis relapse within 6 months and received a second injection in the same knee, 6 patients had available MR sets for the first and the second injections. Four were first injected with IFX and then with MP (3 again relapsed), and 2 first with MP and then with IFX (all again relapsed). None of the reinjected knees showed a significant improvement in knee joint score 4 weeks post-injection (supplementary table 2). In 5 retreated knees (83%) the pre-second injection synovitis scores were again as they were 4 weeks pre-first injection or higher (median Hoffa synovitis scores pre-first injection 2.5 (IQR 1.8;3) and pre-second injection 2.5 (2;3), p=1.000). For effusion score this was seen in all 6 patients (median effusion scores pre-first injection 3 (1.8;3) and pre-second injection 3 (2.5;3), p=1.000).

Table 4. MR improvement after (≥1 points) 4 weeks in relation to early clinical improvement (delta knee joint score ≥1 points) at 4 weeks and relapse after 6 months by treatment with methylprednisolone or infliximab.

Treatment	MR improvement	Early clinical improvement		Relapse	
		yes	no	yes	no
	Hoffa synovitis				
MP*	**yes**	2[#]	2	2	2
	no	4	1	1	4
IFX	**yes**	6	0	6	0
	no	1	3	4	0
	Effusion score				
MP*	**yes**	2[#]	1	2	1
	no	4	2	1	5
IFX	**yes**	5	0	5	0
	no	2	3	5	0

MP: methylprednisolone (no data on early clinical improvement available for 3 injections); IFX: infliximab (no data on early clinical improvement available for 4 injections); MR: magnetic resonance imaging.
*: in 1 patient no Hoffa synovitis and effusion scores available.
[#]: these are the same patients.

Table 5. MRI outcomes and knee joint score in the MP group according to response after 6 months.

Time point	No relapse n=6	Relapse n=6	p-value no relapse vs relapse	p-value week 0 vs. 4 no relapse	p-value week 0 vs. 4 relapse
Hoffa synovitis, median (IQR)					
Baseline	2 (1;2)	2 (2;3)	0.056		
Week 4	1 (1;2)	1.5 (1;2)	0.614		
Delta	0 (-1;0)	0 (-1.5;0.5)		0.157	0.414
Effusion score, median (IQR)					
Baseline	2.5 (1.8;3)	3 (3;3)	0.080		
Week 4	2.0 (1;3)	1.5 (1;2)	0.617		
Delta	0 (-0.5;0)	0 (-1;0)		0.317	0.157
Knee joint score, median (IQR)					
Baseline	3.5 (3.4;4.7)	4.1 (3;5.4)	0.818		
Week 4	1.1 (0.2;2.6)	3.9 (1.6;5.4)	0.114		
Delta	-2.9(-4.3;-0.8)	-0.1 (-0.8;0)		0.028	0.180
Knee tenderness, median (IQR)					
Baseline	1 (1-2)	1 (0-2)	0.589		
Week 4	0.5 (0;1.3)	1 (0.3;2.5)	0.476		
Delta	-1 (-1.3;0.3)	0 (0;0.8)		0.157	0.317
Knee swelling, median (IQR)					
Baseline	2 (2;2.3)	3 (2;3)	0.180		
Week 4	1 (0;1)	2 (1.3;2.8)	0.038		
Delta	-1.5 (-2;-1)	-0.5 (-1;0)		0.024	0.157
VAS score, median (IQR)					
Baseline	0.39 (0.34;0.49)	0.37 (0.15;0.80)	0.818		
Week 4	0.15 (0.03;0.31)	0.35 (0.08;0.64)	0.352		
Delta	-0.24 (-0.46;-0.04)	-0.03(-0.08;-0.01)		0.043	0.109

n: number; IQR: interquartile range

DISCUSSION

We evaluated the signs of synovial inflammation on MR images in patients with chronic or recurrent non-osteoarthritic gonarthritis following intra-articular injection with either infliximab or methylprednisolone. Regardless of type of gonarthritis, similar signs of inflammation using the Hoffa synovitis score and the effusion score were identified in all knees. We found significant changes in MR scores four weeks following intra-articular injection with IFX, but not with MP. These changes appeared to be associated with early clinical response measured with a clinical Knee Joint Score. However, we found no association between pre-injection MR scores or post-injection MR score changes with the clinical response 6 months after either an i.a. IFX or MP injection. All IFX injected knees showed a relapse, compared to 50% of MP injected knees. Relapse was not associated with MR changes, but MP injected knees which showed early clinical improvement may be less likely to clinically relapse after 6 months.

Intra-articular treatment of inflamed joints may often result in rapid symptom reduction.[13-15] This is thought to be due to suppression of local inflammation. However, up to 50% of injected joints still show clinical signs of inflammation or will suffer a clinical relapse after initial improvement.[13] MR is an upcoming imaging tool to detect early stages of damage, arthritis and subclinical arthritis. We hypothesized that signs of inflammation on MR at baseline or after intra-articular injection may be different in knees that do or do not show clinical improvement and/or later relapse. We found that a single dose of 100 mg i.a. IFX appears to be effective on the short term, but is insufficient to induce long-lasting suppression of inflammation, whereas a single dose of 80 mg i.a. MP is less often effective on the short term, but may suppress inflammation possibly longer than IFX.

We can only speculate whether these observations may be related to the mode of action of the i.a. therapies used. Methylprednisolone can cross cell membranes [16] and works intracellularly in contrast to infliximab that binds to extracellular receptors. By inhibiting prostaglandin synthesis and reducing vascular permeability by altering physicochemical properties and the activities of membrane-associated proteins,[16] MP may act through more pathways than infliximab, activating cytokine genes, mediating proinflammatory action of tumor necrosis factor to suppress inflammation and blocking influx of new inflammatory agents.

As an alternative possible explanation of our findings, the dosage of IFX may have been too low to be effective. We used 100 mg IFX per injection as described in successfully treated case reports [2,3,5] but the therapeutic intra-articular dosage may need to be in range with the therapeutic dosage used intravenously.

To our knowledge this is the first study to study changes in signs of inflammation in relation to treatment in arthritic joints. We acknowledge that this was a small exploratory study, where several caveats are due. We included patients with recurrent gonarthritis of various known and unknown origins. Some types or stages of gonarthritis may be irresponsive to MP or IFX

or both. Lacking scoring methods for rheumatoid or other types of arthritis, we used scoring methods developed for osteoarthritis. We found more inflammation in our study compared to previous studies in osteoarthritis patients.[17,18] However, we did not include osteoarthritis patients in our study. We wanted to use gadolinium enhanced MR in all patients, but this was contraindicated or omitted in several patients, in particular in follow up MRs. As a result, we had insufficient data to evaluate possible changes in the Guermazi score. To evaluate clinical response after 4 weeks we used an arbitrary Knee Joint Score, and considered clinical improvement to be represented by a decrease in ≥1 point, which may be under- or oversensitive to measure clinical change in relation to treatment, although in the IFX injected joints it appears to match MR changes.

Our study showed that in patients with gonarthritis of various causes there is a considerable range in severity of features suggesting synovial inflammation as seen on MR and scored with Guermazi, MOAKS and KOSS. Our data suggest that these features are sensitive to change following intra-articular treatment, and that the MR scores originally developed for assessment of osteoarthritis can be used to detect these changes. Larger studies are needed to confirm this. Future studies may also reveal whether this is true for all gonarthritis types, or whether there are differences in relation to the underlying cause of gonarthritis. MR thus may be a promising tool to evaluate, understand and improve intra-articular treatment of our patients with gonarthritis.

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SUPPLEMENTARY FILE

Supplementary table 1: Guermazi MRI outcomes on MRIs preceding injections n=32

	Baseline MRI n=32
Suprapatellar, median (IQR)	1 (1;2)
Infrapatellar, median (IQR)	1 (1;1)
Intercondylar, median (IQR)	1 (0;2)
Adjacent to ACL, median (IQR)	1 (1;1)
Parameniscal lateral, median (IQR)	1 (1;2)
Parameniscal medial, median (IQR)	1 (0;1)
Adjacent to PCL, median (IQR)	1 (0;1)
Loose body, median (IQR)	0 (0;0)

MRI: magnetic resonance imaging; Suprapatellar site: 0.5-1 cm cranial to the superior patellar pole; Infrapatellar site: directly adjacent to the inferior patellar pole; Intercondylar site: at the surface of Hoffa's fat pad 1.5-2 cm distal to inferior patellar pole; ACL: anterior cruciate ligament; Adjacent to ACL site: directly anterior to the ACL close to its femoral attachment; Parameniscal lateral site: directly adjacent posterior to the posterior horn of the lateral meniscus; Parameniscal medial site: directly adjacent posterior horn of the medial meniscus; PCL: posterior cruciate ligament; Adjacent to PCL site: directly adjacent to the PCL at its mid-portion; Loose body: located posteriorly to the PCL; IQR: interquartile range.

Supplementary table 2: MRI outcomes in the 6 patients with cross over in the same knee according to the different randomization groups.

Time point	Total n=12	IFX n=6	MP n=6	p-value	p-value week 0 vs. 4 IFX	p-value week 0 vs. 4 MP
Hoffa synovitis, median (IQR)						
Baseline	2.5 (2;3)	3 (1.8;3)	2 (2;3)	0.476		
Week 4	2 (1;2.8)	2 (1;2.3)	1.5 (1;3)	0.932		
Delta	-1 (-1.5;0)	0 (-1.5;0)	-1 (-1.8;-0.3)		0.102	0.257
Effusion score, median (IQR)						
Baseline	3 (2.3;3)	3 (1.8;3)	3 (2.5;3)	0.598		
Week 4	2.5 (1;3)	2 (1;3)	2.5 (1.8;3)	0.600		
Delta	0 (-1;0)	0 (-1.5;0)	-0.5 (-1;0)		0.180	0.157
Knee joint score, median (IQR)						
Baseline	3.6 (3.2;4.4)	3.6 (2.9;4.5)	3.6 (3;4.6)	0.872		
Week 4	3.3 (2.3;4.2)	3.5 (2.3;4.2)	3.3 (0.8;4.1)	0.618		
Delta	-0.6 (-1;0)	-1 (-1.8;0.6)	-0.05 (-0.8;0)		0.461	0.180
Knee tenderness, median (IQR)						
Baseline	1 (0;1.8)	1 (0;2)	1 (0;1.3)	0.733		
Week 4	1 (0.5;2)	1 (0.5;2)	1 (0.3;1.8)	0.694		
Delta	0 (-0.8;0.8)	-0.5 (-1;0.8)	0 (0;0.8)		0.336	0.109
Knee swelling, median (IQR)						
Baseline	2 (2;3)	2 (2;3)	2.5 (2;3)	0.575		
Week 4	2 (1;2)	2 (1.5;2)	1.5 (0.3;2.8)	0.686		
Delta	-0.5 (-1;0)	-0.5 (-1;0)	-0.5 (-1;0)		0.458	0.458
VAS score, median (IQR)						
Baseline	0.34 (0.19;0.40)	0.27 (0.14;0.48)	0.35 (0.15;0.51)	0.687		
Week 4	0.28 (0.17;0.35)	0.26 (0.17;0.40)	0.31 (0.08;0.36)	0.623		
Delta	-0.03 (-0.08;0)	-0.05 (-0.09;0.05)	-0.03 (-0.05;-0.01)		0.498	0.686

IFX: infliximab; MP: methylprednisolone; n: number; IQR: interquartile range.

Chapter 6

EFFECTIVENESS OF FOUR DYNAMIC TREATMENT STRATEGIES IN PATIENTS WITH ANTI-CITRULLINATED PROTEIN ANTIBODY-NEGATIVE RHEUMATOID ARTHRITIS – A RANDOMISED TRIAL

Gülşah Akdemir*, Iris M. Markusse*, Linda Dirven, Nagmeh Riyazi, Gerda M. Steup-Beekman, Pit J.S.M. Kerstens, Willem F. Lems, Tom W.J. Huizinga, Cornelia F. Allaart

*both authors contributed equally

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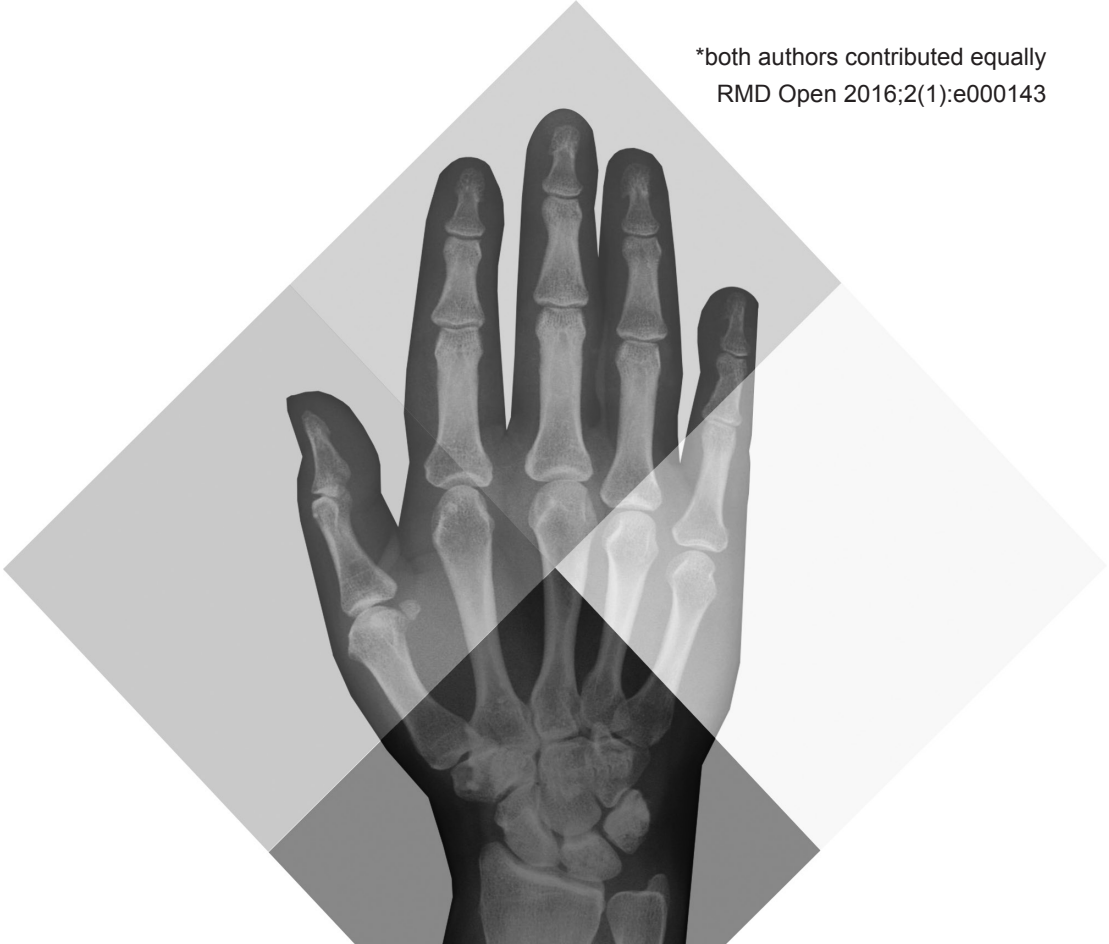

ABSTRACT

Objective

To determine the most effective treatment strategy among anti-citrullinated protein antibodies (ACPA)-negative early rheumatoid arthritis patients.

Methods

In the BeSt study, 184 ACPA-negative patients were randomized to 1. sequential monotherapy, 2. step-up therapy, 3. initial combination including prednisone, 4. initial combination including infliximab. Treatment was targeted at disease activity score (DAS) ≤2.4. Early response and 10-year outcomes were compared between the four strategy-arms in ACPA-negative patients.

Results

ACPA-negative patients achieved more short-term functional improvement on initial combination therapy than on monotherapy (at month 3 mean Health Assessment Questionnaire[HAQ] 0.71 versus 0.98, p=0.006; at month 6 0.59 versus 0.87, p=0.004). Functional ability over time was comparable between the strategy-arms(p=0.551) with a mean HAQ of 0.6 at year 10 (p=0.580 for comparison across the strategy-arms). 10-year radiographic progression was negligible (median 0.5) and comparable between the 4 strategy-arms (p=0.082). At year 10, remission was achieved by 11/40 (28%), 9/45 (20%), 17/56 (30%) and 17/43 patients (40%) in strategy-arms 1 to 4, respectively (p=0.434). Over time similar remission percentages were achieved in all strategy-arms (p=0.815). 18%,16%,20% and 21% in strategy-arms 1 to 4(p=0.742) were in drug-free remission at year 10, with a median duration of 60 months across the arms.

Conclusions

Initial combination therapy with methotrexate, sulfasalazine and prednisone, or methotrexate and infliximab, is the most effective treatment strategy for ACPA-negative patients, resulting in earlier functional improvement than initial methotrexate monotherapy. After 10 years of targeted treatment, in all strategy-arms favourable clinical outcomes were achieved and radiographic progression was limited.

INTRODUCTION

In patients with rheumatoid arthritis (RA), presence of anti-citrullinated protein antibodies (ACPA) is associated with worse clinical and radiographic outcomes, compared to ACPA-negative RA.[1-6] It has been proposed that ACPA-negative RA is another disease entity than ACPA-positive RA [7-9] and therefore requires a different treatment approach.[10] However, it is not clear which treatment strategy, in particular which initial treatment choice, is most effective in ACPA-negative RA patients. ACPA-negative patients have been suggested to not require combination therapy and not benefit from corticosteroids,[10] but respond better to anti-tumour necrosis factor alpha (anti-TNFα) agents than ACPA-positive patients.[11-13]
In the BeSt study, recent-onset active RA patients were included and treated without ACPA status being known. Patients were randomized to one of four dynamic treatment strategies, all aiming to achieve low disease activity (Disease Activity Score: DAS≤2.4). In a previous analysis of the BeSt study we found that there were no significant differences in clinical response between ACPA-negative and ACPA-positive patients.[6] Here, we aim to determine in further detail what the most effective treatment strategy is for ACPA-negative patients. We investigated which treatment strategy resulted in the most rapid clinical response and the most favourable long-term clinical and radiographic outcomes for ACPA-negative patients.

PATIENTS & METHODS

Study design and patients
The BeSt study (Dutch acronym for treatment strategies), a multicentre randomized clinical trial, enrolled 508 patients to compare four dynamic treatment strategies in patients with active (at least 6 inflamed joints and either a high ESR or a high patient VAS for disease activity) recent-onset RA according to the 1987 revised American College of Rheumatology (ACR) criteria.[14] More study details were previously published.[15,16] The medical ethics committees of all participating centers approved the study protocol and all patients gave written informed consent.
Patients were randomized to: 1. sequential monotherapy, 2. step-up combination therapy, 3. initial combination including prednisone, 4. initial combination including infliximab. Strategy arm 1 and 2 both started with methotrexate (MTX) monotherapy. In strategy arm 3, patients started with MTX, sulfasalazine (SSA) and prednisone, and in strategy arm 4, patients received MTX and infliximab. Every three months disease activity scores (DAS) were measured. Treatment was targeted at low disease activity (DAS≤2.4). If low disease activity was not achieved, the next treatment step was taken. In case the DAS was ≤2.4 for ≥6 months, medication was tapered to a maintenance dose. If the DAS was then <1.6 for ≥6 months, medication was

discontinued. As soon as DAS was ≥1.6, medication was restarted, and further treatment steps were taken if DAS was >2.4 at a later visit.
ACPA were determined in a research setting using the anti-cyclic citrullinated peptide (anti-CCP2) test, in 484 available serum samples that were collected at baseline and stored; for the remaining 24 patients no serum sample was available. ACPA status did not influence treatment instructions according to the study protocol. For the current post hoc-analysis, results of the four treatment strategies were compared within ACPA-negative patients.

Study endpoints

Primary outcomes were functional ability and radiographic joint damage progression. Functional ability was measured three-monthly with the health assessment questionnaire (HAQ, range 0-3).[17] Radiographic joint damage was assessed on radiographs of hands and feet, using the Sharp van der Heijde score (SHS, range 0-448).[18] Radiographs were obtained yearly and were assessed in one session by two trained readers, blinded for patient identity, strategy arm and time order. Progression as a continuous measure was defined as an increase in SHS between two subsequent time points. Absence of progression was defined as <0.5 units increase in SHS and presence as ≥0.5 units increase in SHS.
DAS-remission percentages (defined as DAS<1.6 [19]), drug-free remission (DFR) percentages, toxicity and treatment response were secondary outcomes in this study. Toxicity included all reported (serious) adverse events ((S)AE). Treatment response to initial monotherapy and initial combination therapy were described for year 1 and 2 of follow-up. Treatment response was defined as success or failure on a specific treatment step. Success was defined as achieving and maintaining a DAS≤2.4 and failure was defined as a persistent DAS>2.4 or discontinuation of medication due to toxicity.
Early response was defined based on improvement in functional ability and the percentage of DAS-remission from three months after treatment start up to year 1. Radiographic progression during the first year was compared among the strategy arms. Long-term effect of the strategy arms was assessed based on the primary and secondary outcomes measured every three months or (for radiographic progression) yearly up to year 10.

Statistical analyses

Baseline characteristics and outcomes after 10 years were compared between the different treatment arms by the χ^2 test, independent *t* test and ANOVA, as appropriate. For the non-Gaussian distributed outcomes the Kruskal-Wallis test or Mann-Whitney *U* test were used.

HAQ was compared at 3, 6, 9 and 12 months between the initial monotherapy arms (arm 1 and 2 combined) and the initial combination therapy arms (arm 3 and 4 combined) with an independent *t* test. Previous publications showed that arm 1 and 2 (monotherapy arms) had

a similar response, and also responses in arm 3 and 4 (combination therapy arms) were comparable.[15,20] Furthermore, HAQ was longitudinally analysed with linear mixed models (LMM). Determinants used for all longitudinal analysis were treatment group, time and its interaction term. This analysis was performed twice: first over 1 year follow-up (0-1 year) to determine early response, next over the ten year follow-up (0-10 year) to determine long-term outcomes. Generalized linear mixed models (GLMM) were used to analyse differences in DAS-remission percentages. Treatment group, time and its interaction term were entered as determinants. This analysis was also performed twice; for 0-1 year and for 0-10 year follow-up. The dropout rates were compared between the different treatment groups using Kaplan-Meier curves. Responses to the first, second and third treatment step in strategy arms 1 and 2, expressed as drug survival, were shown in Kaplan-Meier curves.

SHS progression during the first year was compared with a Kruskal-Wallis test. SHS progression over ten years was depicted in a cumulative probability plot, stratified for treatment strategy. SHS progression over time was analysed using a GLMM with SHS progression as binary outcome (defined as delta ≥0.5 units per year yes/no). Treatment strategy, time and its interaction were entered as determinants.

On the one hand, the power calculation of the BeSt study was based on the total study population, and we here only include a subpopulation (184 of 508). On the other hand, we performed multiple comparisons. These effects indicate that the p-values should be interpreted in opposite directions. Therefore, we decided to adjust for neither of the effects.

RESULTS

Baseline characteristics for 184 ACPA-negative patients (of 508 patients included in the BeSt study) were similar in the strategy arms. In correspondence to the inclusion criteria, disease activity was high (mean ± SD DAS 4.6 ± 0.9) and functional ability considerably impaired (mean ± SD HAQ 1.5 ± 0.7) (Table 1). During ten years follow-up, 71/184 patients (39%) dropped out of the study, equally distributed among the strategy arms (p=0.738). 125/184 patients were both ACPA and rheumatoid factor (RF)-negative. Also for these, there were no significant differences in baseline characteristics between the treatment arms (supplementary table 1), nor in comparison with ACPA-negative and RF-positive patients (data not shown).

Table 1: Baseline characteristics

	Sequential monotherapy	Step-up therapy	Initial combination with prednisone	Initial combination with infliximab
	N = 40	N = 45	N = 56	N = 43
Age (years), mean ± SD	56 ± 15	53 ± 15	57 ± 13	53 ± 16
Female, n (%)	30 (75)	36 (80)	38 (68)	32 (74)
Symptom duration (weeks), median (IQR)	19 (12-41)	30 (16-52)	22 (11-41)	19 (13-31)
DAS, mean ± SD	4.6 ± 0.9	4.7 ± 0.8	4.5 ± 0.8	4.6 ± 1.0
HAQ, mean ± SD	1.5 ± 0.7	1.4 ± 0.5	1.5 ± 0.6	1.5 ± 0.8
RF positive, n (%)	12 (30)	12 (27)	22 (39)	13 (30)
Erosive disease, n (%)	27 (68)	28 (62)	36 (64)	28 (65)
Smoker, n (%)	14 (35)	11 (24)	16 (29)	10 (23)

DAS: disease activity score; HAQ: health assessment questionnaire (scale 0-3); Erosive disease: >0.5 erosion score on radiographs of hands and feet based on the Sharp van der Heijde score. Radiographs were assessed by two independent readers, and the mean score of both readers was used.; IQR, interquartile range; RF: IgM rheumatoid factor; SD, standard deviation.

Early response

During the first year, functional ability improved earlier in patients treated with initial combination therapy (arm 3 and 4) than in patients treated with initial monotherapy (arm 1 and 2) (Figure 1A). After 3 months mean (SD) HAQ was 0.98 (0.63) in the monotherapy arms vs. 0.71 (0.64) (p=0.006) in the combination therapy arms and after 6 months 0.87 (0.68) versus 0.59 (0.57) (p=0.004). In the monotherapy arms 64% of patients had a HAQ improvement >0.22 points (minimal important difference [21]) after 3 months and 68% after 6 months, compared to 81% of patients and 82%, respectively, in the combination therapy arms (p=0.012 at 3 months and p=0.026 at 6 months). Probably as a result of continued DAS≤2.4 targeted treatment adjustments, from 9 months of follow-up onwards, no differences in functional ability were found between the strategy arms. At 9 months, mean (SD) HAQ was 0.81 (0.71) in the monotherapy arms and 0.63 (0.57) in the combination therapy arms (p=0.067), and at year 1 these numbers were 0.69 (0.69) and 0.57 (0.54) (p=0.195), respectively. In 'double negative'(ACPA-negative and RF-negative) patients early decrease in HAQ was seen in all strategy arms and was significantly different between monotherapy arms and combination therapy arms at 3 months (p=0.024) (supplementary table 2). If the monotherapy arms and combination therapy arms were combined HAQ improved earlier in patients treated with combination therapy at 3 and 6 months (p=0.003 and p=0.010, respectively (supplementary table 3).

In the longitudinal analysis, over the first year of follow-up, level of functioning was similar between the four strategy arms (p=0.236). For 'double negative' patients, similar results were obtained (data not shown).

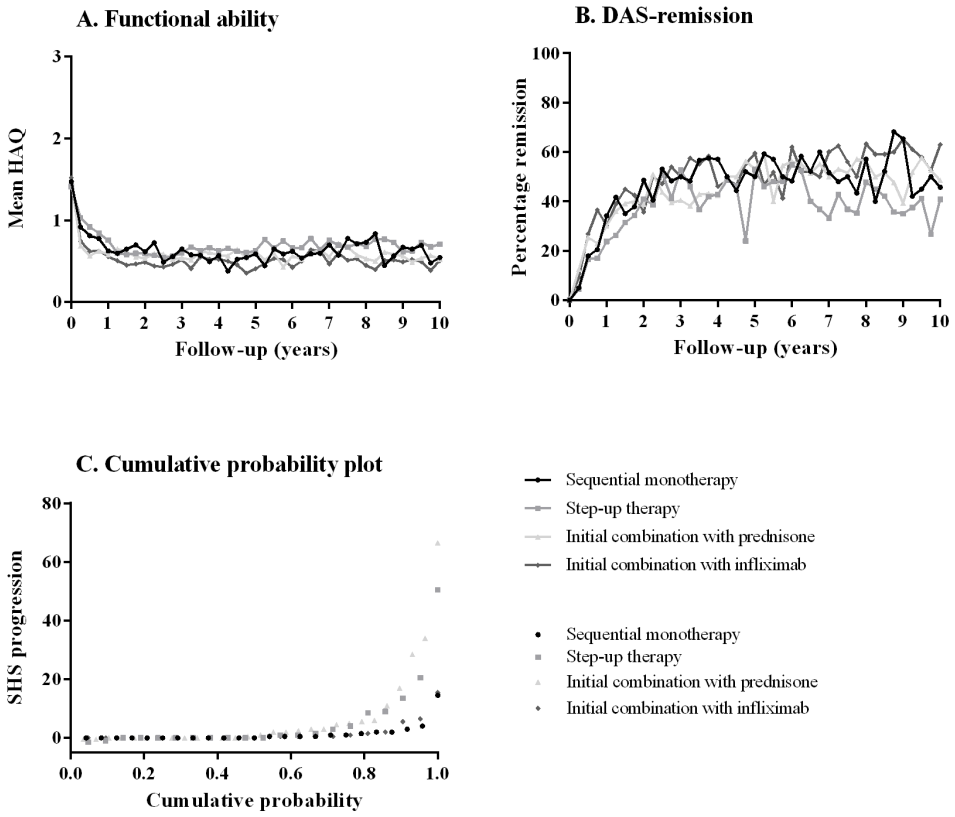

Figure 1: Functional ability (A), DAS-remission percentages (B) and probability plot of radiographic joint damage progression (C) from baseline to year 10 (completer analysis)

Notes Figure 1B: DAS-remission was defined as disease activity score (DAS) <1.6.[19] Percentages reflect the number of patients in DAS-remission as part of the completers. More patients missed the visits before the yearly visits at year 5 and 10, because they were running behind on their schedule. Low attendance make the DAS-remission percentages at these visits difficult to interpret. Mean disease activity did not show this decrease (data not shown).

Notes Figure 1C: Patients in strategy arm 1 and 4 had numerically less progression compared to strategy arm 2 and 3, although not statistically significant (p=0.639). In strategy arm 1 and 4 patients with progression (defined as ≥0.5 SHS) had moderate disease activity during early visits (mean DAS ± SD 2.99 ± 1.14 at 3 months and 2.45 ± 1.13 at 6 months) and 46% was rheumatoid factor (RF) positive. In strategy arm 2 and 3 patients with progression (defined as ≥0.5 SHS) had also moderate disease activity at early visits (mean DAS ± SD 2.99 ± 1.16 at 3 months and 2.46 ± 1.14 at 6 months) and 42% was RF-positive.

HAQ: health assessment questionnaire (range 0-3); SHS: Sharp van der Heijde score.

During the first year, higher percentages of DAS-remission (DAS<1.6) were found in strategy arms 3 and 4 than in strategy arms 1 and 2, although not significantly different (Figure 1B): after 3 months 5% in the monotherapy arms compared to 11% in the combination therapy arms achieved DAS-remission (p=0.119); after 6 months 17% versus 25% (p=0.161); after 9

months 18% versus 27% (p=0.116) and after 1 year 27% versus 29% (p=0.833). Over the first year, no differences were found between the four strategy arms (p=0.472).
Radiographic progression during year 1 was low as expected, with median (IQR) progression scores of 0 (0-0), 0 (0-1), 0 (0-1) and 0 (0-0.5) in strategy arms 1 to 4, respectively (p=0.259).

Long-term outcomes

At year ten, mean (SD) DAS has decreased from 4.6 (0.9) at baseline to 1.6 (0.8) and HAQ from 1.5 (0.7) to 0.6 (0.6) (more details in Table 2). Over ten year time, no differences in clinical outcomes were found. Functional ability was similar among the four strategy arms (p=0.551) (Figure 1A). The same was true for DAS-remission percentages (p=0.851) (Figure 1B). Similar results were obtained for double negative patients (data not shown). There was no difference in CDAI, DAS and HAQ during 10 years follow-up for patients that were treated with steroids from the beginning (arm 3) versus patients that were not treated with steroids from the beginning (arm1, 2 and 4) (data not shown).

Table 2: Clinical and radiographic outcomes in the different strategy arms at year 10.

	Sequential monotherapy	Step-up therapy	Initial combination with prednisone	Initial combination with infliximab	p value
	N = 40	N = 45	N = 56	N = 43	
Drop out, n (%)	14 (35)	20 (44)	21 (38)	16 (37)	0.738
DAS, mean ± SD	1.7 ± 0.9	1.8 ± 0.8	1.6 ± 0.8	1.4 ± 0.8	0.431
HAQ, mean ± SD	0.5 ± 0.5	0.7 ± 0.7	0.5 ± 0.5	0.5 ± 0.5	0.580
DAS-remission, n (%)	11 (28)	9 (20)	17 (30)	17 (40)	0.434
Drug-free remission, n (%)	7 (18)	7 (16)	11 (20)	9 (21)	0.742
On initial treatment step, n (%)	10 (25)	7 (16)	18 (32)	15 (35)	0.161
Use of infliximab, n (%)	3 (8)	3 (7)	4 (7)	4 (9)	0.978
Use of prednisone, n (%)	0 (0)	0 (0)	3 (5)	2 (5)	0.226
SHS progression, year 0-10 Median (IQR)	0.3 (0 - 1.4)	0 (0 - 6.3)	1.0 (0 - 5.3)	0 (0 - 1.3)	0.639
SHS progression ≥5 units, n (%)	1 (3)	5 (11)	8 (14)	3 (7)	0.132
SHS progression ≥10 units, n (%)	1 (3)	3 (7)	5 (9)	1 (2)	0.324

DAS: disease activity score; HAQ: health assessment questionnaire (scale 0-3); SHS: Sharp van der Heijde score; IQR, interquartile range; SD, standard deviation.

During ten years, drug-free remission was ever achieved by 16/40 (40%), 15/45 (33%), 20/56 (36%) and 21/43 patients (49%) in strategy arms 1 to 4, respectively (p=0.453). In 5/16, 4/15, 6/20 and 7/21 patients in strategy arms 1 to 4, respectively (p=0.993), DFR was lost during follow-up. Of these patients 4/5, 3/4, 2/6 and 3/7 patients in strategy arms 1 to 4, respectively (p=0.704) achieved clinical DAS-remission again, with a median (IQR) of 1.0 (0.3-3.5) since loss of DFR. Only 1 patient in strategy arm 3 and 2 patients in strategy arm 4 achieved DFR after restart of medication. Table 2 shows DFR percentages at year 10.

Median (IQR) total SHS progression after 10 years of targeted treatment was low and similar between the four treatment groups in the study completers (p=0.639) (Table 2). Figure 1C shows the cumulative probability of SHS progression per strategy arm in ACPA-negative patients who completed follow-up. Over time, based on a generalized linear mixed model that takes into account all included patients, no difference in SHS progression (defined as delta ≥0.5 units per year) was found between the randomization strategy arms: with strategy arm 1 as reference, odds ratios (95% confidence interval) were 1.98 (0.60-6.47) for arm 2, 2.89 (0.96 – 8.72) for arm 3 and 1.66 (0.50-5.47) for arm 4 (p=0.082).

Response to initial monotherapy

Response to initial monotherapy in strategy arms 1 and 2 was explored during year 1 and 2. Eighteen out of 84 patients (21%) achieved the treatment target of low disease activity after three months, but 64/84 patients (76%) failed to respond to initial MTX monotherapy (and had to increase MTX dose according to the study protocol). Two patients stopped MTX because of an AE (nausea and headache) (Figure 2A). At 6 months, 39/84 patients (46%) achieved a DAS≤2.4 on MTX monotherapy. Thirty six patients failed due to a DAS>2.4 (despite MTX dose increase at 3 months) and 2 patients failed due to an AE (not specified).

The second treatment step was taken in 46/84 patients: switching to (in strategy arm 1) or adding (in strategy arm 2) SSA. In 9/46 patients (20%) a DAS≤2.4 was achieved on this step (Figure 2B). Failure on SSA therapy occurred in 33/46 patients because of a DAS>2.4 and in 4/46 patients because of an AE (skin/mucous, infection, nausea and malaise).

In total, 35/84 patients continued to the third treatment step during 2 years of follow-up: switching to leflunomide monotherapy (in strategy arm 1) or adding hydroxychloroquine to MTX and SSA (in strategy arm 2). In 9/35 patients (26%) a DAS≤2.4 was achieved (Figure 2C). During 2 years of follow-up, 21/35 patients (60%) continued to the next treatment step due to a DAS>2.4. Five patients failed due to an AE (3 times gastro-intestinal, malaise and skin/mucous). DAS-components that contributed to failure due to DAS>2.4 per treatment step are shown in supplementary table 4.

After 1 year, 7/40 patients (18%) in strategy arm 1 continued to combination therapy (MTX and infliximab). During year 2, two additional patients continued to combination therapy. In strategy arm 2, 24/45 patients (53%) used combination therapy (MTX and SSA, step 3 in the study protocol) at the end of year 1. During year 2, only one more patient failed on monotherapy and continued to combination therapy. The difference in percentages combination therapy between strategy arms 1 and 2 can be explained by the design of the protocol: in strategy arm 1, the first option to receive combination therapy was the 3rd step after initial MTX treatment, while it was already the 2nd step in strategy arm 2.

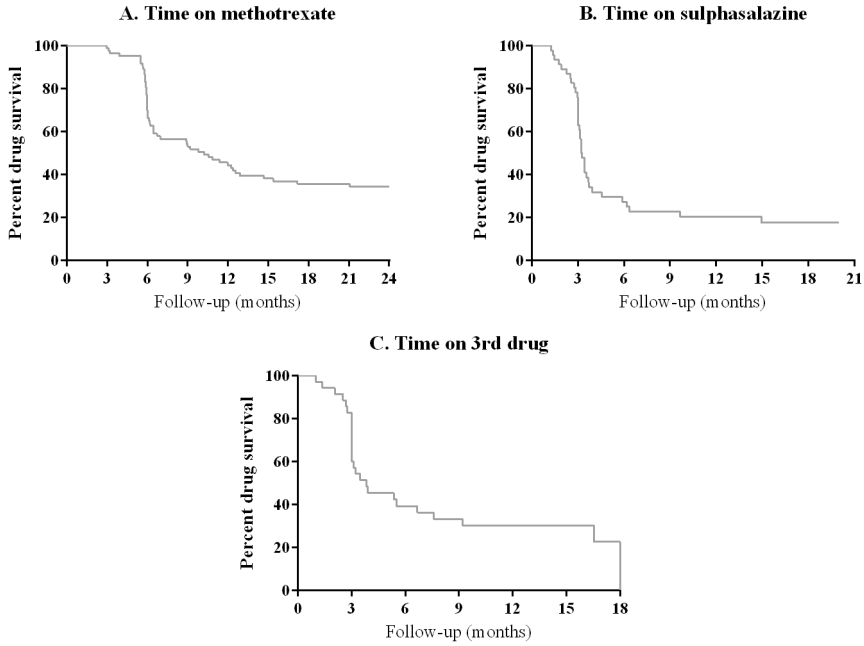

Figure 2: Kaplan-Meier Curves showing drug survival in strategy arms 1 and 2.
A: Initial methotrexate monotherapy, n=84, B. Switching to sulphasalazine monotherapy in strategy arm 1, adding sulphasalazine to methotrexate in strategy arm 2, n=46, C. Switching to leflunomide monotherapy in strategy arm 1, adding hydroxychloroquine to methotrexate and sulphasalazine in strategy arm 2, n=35. Discontinuation of drugs is due to insufficient response, toxicity or other reasons. The lines indicate the percentage of patients in strategy arm 1 and 2 that are treated according to the concerned treatment step.

Response to initial combination therapy

By the end of year 1, in strategy arm 3 (MTX, SSA and prednisone) 18/56 patients (32%) had tapered combination therapy to monotherapy of which 3 restarted with MTX during the second year. In strategy arm 4, 17/43 patients (40%) had discontinued infliximab. One of them restarted infliximab during the second year. For more detailed treatment responses to initial combination therapy during 2 year follow-up (strategy arms 3 and 4) flowcharts are shown in the supplementary file (Supplementary Figure 1 and 2).

Toxicity

During ten years of follow-up in total 1,265 adverse events (AE) were reported in 36/40, 39/45, 55/56 and 41/43 patients in strategy arms 1 to 4, respectively (p=0.113). The most common AE in all groups were upper airway infections, elevated liver enzymes, nausea and other gastro-intestinal complaints. SAE were reported in 25/40, 29/45, 27/56, and 22/43 patients in strategy arms 1 to 4, respectively (p=0.300) (Table 3). Ten patients died during the study; one in strategy arm 1, four in strategy arm 2, one in strategy arm 3 and four in strategy arm 4

(p=0.220) (details in Table 3). (S)AE during year 1, when most patients in strategy arms 3 and 4 were still on combination therapy, are reported in Table 3.

Table 3: Number of reported adverse events and serious adverse events.

	Sequential monotherapy	Step-up combination therapy	Initial combination with prednisone	Initial combination with infliximab	p value
	N = 40	N = 45	N = 56	N = 43	
0-1 year follow-up					
AE, n*	31	51	41	34	0.414
SAE, n*	3	3	6	1	0.400
0-10 year follow-up					
Total AE, n*	293	292	368	312	0.872
Patients with AE, n (%)	36	39	55	41	0.113
Total SAE, n*	50	33	60	43	0.183
Patients with SAE, n (%)	25 (63)	19 (42)	27 (48)	22 (51)	0.300
Patients with serious infection, n (%)	9 (23)	5 (11)	5 (9)	3 (7)	0.124
Patients with malignancy, n (%)	3 (8)	2 (4)	8 (14)	6 (14)	0.310
Deceased, n**	1	4	1	4	0.220

*More events per patient possible
** Causes of death, group 1: 1 ischemic colon after complicated diverticulitis surgery; group 2: 1 lung carcinoma, 1 stomach cancer, 2 unknown; group 3: 1 lung carcinoma; group 4: 1 esophagus carcinoma, 1 cardiac arrest, 1 lung carcinoma, 1 unknown
AE: adverse event; SAE: serious adverse event.

DISCUSSION

Previous literature suggests that ACPA-negative and ACPA-positive RA patients may represent two different disease entities, which may require different treatment strategies.[7-10] On one hand, as ACPA-negative patients are less likely to develop joint damage and more likely to achieve drug-free remission,[2,5,6,22] they may not need intensive treatment. On the other hand, with similar disease activity, functional disability is not related to ACPA status[6,23] and to alleviate symptoms rapidly, the initial treatment choice is important. Roughly 50% of active RA patients fail to achieve low disease activity within 6 months on methotrexate monotherapy.[24] In RA (2010 criteria) and UA patients in the PROMPT study, we showed that methotrexate was as effective as placebo in ACPA-negative patients.[25] To establish the best initial treatment strategy in ACPA-negative RA patients, we performed the current analysis in the BeSt study. Based on our results, all four strategy arms starting with either monotherapy or combination therapy have a comparable long-term effectiveness, with the only difference that an earlier functional improvement was achieved following initial combination therapy with

the option to taper to monotherapy. Radiographic progression was generally low as expected in ACPA-negative patients and after 10 years of targeted treatment without difference between the strategy arms.

These results expand on our previous report that compared clinical response between ACPA-positive and ACPA-negative patients in the BeSt study.[6] Initial combination therapy appears to result in earlier clinical response in both groups of patients, and during subsequent treatment adjustments targeted at low disease activity (DAS≤2.4), clinical outcomes are roughly similar from month 9 of follow-up onwards. In this analysis, we showed that also ACPA-negative patients benefit from initial combination therapy, with a better functional ability at 3 and 6 months follow-up compared to patients treated with initial methotrexate monotherapy. This was also seen in seronegative (ACPA-negative and RF-negative) patients. This indicates that RF does not seem to predict treatment response. In ACPA-positive and ACPA-negative patients, treatment choices depend on positive effects that one aims to achieve, in relation to possible negative effects. If treatment aims mainly at preventing long-term debilitating joint damage, one may argue that ACPA-negative patients require less intensive treatment and maybe a less stringent treatment target, than ACPA-positive patients. Likewise ACPA-positive patients may require more intensive treatment and possibly a more stringent treatment target. If rapid relief of symptoms is the aim of initiating treatment, then initial combination therapy has the highest success rate. In the BeSt study, all patients were selected on having active RA, with ≥6/66 swollen and ≥6/68 painful joints and either an ESR>28 mm/hr or a high VAS (≥20 mm) of global health. At baseline, ACPA-negative patients had an even slightly higher DAS and more severe functional disability than ACPA-positive patients.[6] Compared to the 1987 criteria used in the BeSt study, the 2010 criteria instigate that primarily ACPA-negative patients with high tender and swollen joint counts will be classified as having RA.

Rapid symptom relief, associated with less work disability [26] is an important treatment target. We have shown that only the minority of ACPA-negative patients respond to MTX monotherapy (despite a dose increase after three months), and that in case of failure, the response to SSA is even poorer. DAS components revealed a substantial inflammatory element in these failing patients. In contrast, a rapid decrease in disease activity is observed following initial combination therapy, with accompanied improvement in functional ability. These results point towards the favourable effects of initial combination therapy in patients with ACPA-negative RA. Registration of AEs and SAEs during the BeSt study did not show more toxicity in the initial combination strategy arms than in the initial monotherapy arms.[16] This may be related to the fact that after a rapid improvement, tapering and discontinuation was often possible: tapering at the earliest possibility of prednisone in strategy arm 3 (at week 28) was possible in 66% of patients, and 32% subsequently tapered to SSA monotherapy. In strategy arm 4 discontinuation of infliximab to MTX monotherapy (by protocol possible first at month 9) occurred in 33% of patients, and after 12 months in 40%. To meet concerns on possible

adverse effects of high-dose corticosteroids, although not objectified in this trial, more recent studies have shown that the initial dose of prednisone may not need to be as high and as was used in the COBRA trial [27] and subsequently in the BeSt study to achieve similar rapid suppression of disease activity.[28-30]

Given the fact that our data are derived from a subpopulation of the BeSt trial, there are several caveats. First, in the smaller ACPA-negative population, in relation to the power calculations done for the complete BeSt population, we may not have had sufficient power to detect differences between the treatment arms. In part to overcome this, we combined the results of arms 1 and 2, which used the same medication for the first 6 months of the trial, and of arms 3 and 4. Although small numbers and lack of power may have resulted in underestimation of any difference between treatment strategies, the significant differences between the 3-6 months efficacy of initial monotherapy and initial combination therapy remain. Second, the BeSt study only included patients with a high disease activity, including at least 6/66 swollen and 6/68 painful joints and either a high ESR or a high patient VAS for disease activity. Thus, it is unclear whether our conclusions would apply for ACPA-negative patients with less active disease. If symptoms are mild and functional impairment slight, patients may want to risk a delay in improvement to avoid combination therapy.

In conclusion, for ACPA-negative RA patients, initial combination therapy with methotrexate and either sulfasalazine plus prednisone, or infliximab is the most effective treatment strategy. It results in earlier functional improvement, without additional adverse events, than initial methotrexate monotherapy. We suggest that treatment of all patients with early and active RA should focus on rapid relief of symptoms, and that there is no reason to weigh the initial treatment choice based on the presence of ACPA.

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SUPPLEMENTARY FILE

Supplementary table 1: Baseline characteristics and primary outcomes at year 1 and year 10 for RF-negative and ACPA-negative patients.

	Sequential monotherapy	Step-up therapy	Initial combination with prednisone	Initial combination with infliximab	p-value
	n=28	n=33	n=34	n=30	
Baseline					
Age (years), mean ± SD	55±13	54±16	58±14	55±15	
Female, n (%)	20 (71)	28 (85)	19 (56)	21 (70)	
Symptom duration (weeks), median (IQR)	19 (11-41)	27 (15-46)	22 (12-45)	22 (14-43)	
DAS, mean ± SD	4.9±0.9	4.7±0.9	4.5±0.9	4.5±1.1	
HAQ, mean ± SD	1.5±0.7	1.4±0.6	1.5±0.7	1.5±0.8	
Erosive disease, n (%)	19 (68)	22 (67)	21 (62)	22 (73)	
Smoker, n (%)	10 (36)	6 (18)	9 (26)	7 (23)	
Year 1					
SHS progression, median (IQR)	0 (0-0)	0 (0-0.9)	0 (0-1)	0 (0-0.5)	0.206
Year 10					
DAS, mean ± SD	1.6±1.0	1.7±0.8	1.4±0.9	1.3±0.8	0.090
HAQ, mean ± SD	0.6±0.6	0.6±0.7	0.5±0.5	0.6±0.4	0.575
DAS-Remission, n (%)	9 (32)	7 (21)	12 (35)	12 (40)	0.606
SHS progression, median (IQR)	0 (0-0.5)	0 (0-3.5)	0 (0-2.8)	0 (0-0.6)	0.762

ACPA: anti-citrullinated protein antibodies; RF: IgM rheumatoid factor; DAS: disease activity score; HAQ: health assessment questionnaire (scale 0-3); Erosive disease: >0.5 erosion score on radiographs of hands and feet based on the Sharp van der Heijde score. Radiographs were assessed by two independent readers, and the mean score of both readers was used; SHS: Sharp van der Heijde score; IQR, interquartile range; SD, standard deviation.

Supplementary table 2: Functional ability and DAS-remission percentages during the first year for RF-negative and ACPA-negative patients according to the 4 strategy arms.

	Sequential monotherapy	Step-up therapy	Initial combination with prednisone	Initial combination with infliximab	p-value
	n=28	n=33	n=34	n=30	
HAQ, mean ± SD					
3 months	1.04±0.69	1.06±0.69	0.74±0.63	0.65±0.53	0.024
6 months	0.92±0.77	0.88±0.69	0.58±0.52	0.60±0.60	0.076
9 months	0.88±0.70	0.79±0.81	0.63±0.57	0.57±0.50	0.258
12 months	0.75±0.71	0.70±0.81	0.61±0.57	0.51±0.48	0.531
DAS-remission, n (%)					
3 months	1 (4)	1 (3)	3 (9)	4 (13)	0.417
6 months	5 (18)	6 (18)	8 (24)	8 (27)	0.806
9 months	5 (18)	6 (18)	6 (18)	11 (37)	0.210
12 months	9 (32)	8 (24)	9 (27)	11 (37)	0.805

ACPA: anti-citrullinated protein antibodies; RF: IgM rheumatoid factor; DAS: disease activity score; HAQ: health assessment questionnaire (scale 0-3).

Supplementary table 3: Functional ability and DAS-remission percentages during the first year for RF-negative and ACPA-negative patients according to monotherapy and combination therapy.

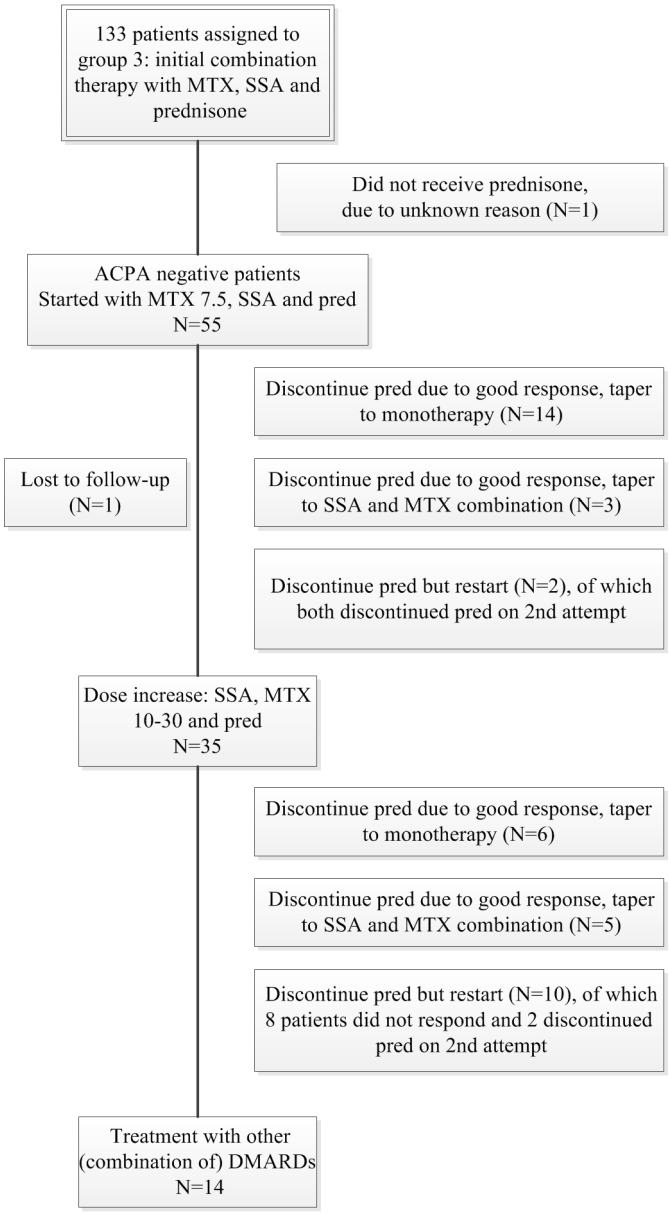
	Monotherapy	**Combination therapy**	**p-value**
	n=61	**n=64**	
HAQ, mean ± SD			
baseline	1.5±0.6	1.5±1.7	0.934
3 months	1.05±0.68	0.70±0.58	0.003
6 months	0.90±0.72	0.59±0.58	0.010
9 months	0.83±0.75	0.60±0.53	0.055
12 months	0.73±0.76	0.56±0.53	0.188
DAS-remission, n (%)			
3 months	2 (3)	7 (11)	0.166
6 months	11 (18)	16 (25)	0.370
9 months	11 (18)	17 (27)	0.252
12 months	17 (28)	20 (31)	0.824

ACPA: anti-citrullinated protein antibodies; RF: IgM rheumatoid factor; DAS: disease activity score; HAQ: health assessment questionnaire (scale 0-3).

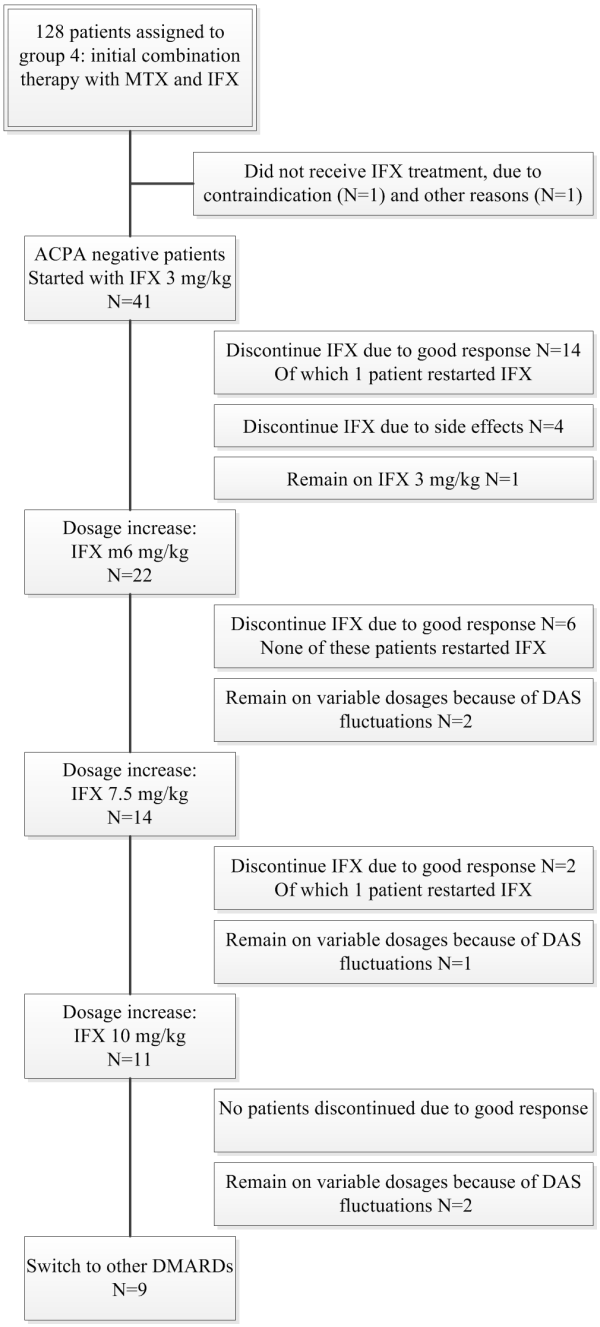
Supplementary table 4: Components of the disease activity score in patients who failed on the treatment steps in strategy arms 1 and 2, both starting with methotrexate monotherapy.

	Failure on MTX at 3 months	**Failure on MTX at 6 months**	**Failure on SSA at 9 months**	**Failure on step 3 at 12 months**
	15 mg weekly	*25 mg weekly*		
	N=64	N=36	N=33	N=21
SJC	9 (4-14)	9 (4-12)	6 (2-10)	4 (3-11)
TJC	11 (7-16)	12 (8-17)	9 (5-17)	10 (7-16)
ESR	22 (12-32)	20 (13-29)	20 (14-41)	21 (12-24)
VAS	37 (20-51)	47 (26-55)	48 (25-69)	40 (20-65)

Numbers indicate median (interquartile range).
SJC: 44 swollen joint count; TJC: tender joint count (Ritchie articular index); ESR: erythrocyte sedimentation rate; VAS: patient's assessment of global health on a visual analogue scale (0-100 mm); MTX: methotrexate monotherapy; SSA: sulfasalazine (switching to SSA monotherapy in strategy arm 1, adding SSA to MTX in strategy arm 2); Step 3: leflunomide in strategy arm 1, adding hydroxychloroquine to MTX and SSA in strategy arm 2.



Supplementary figure 1: Flowchart of randomization arm 3 (initial combination with methotrexate, sulphasalazine and prednisone) during year 1 and 2 of follow-up, stratified for ACPA-status.
ACPA, anti-citrullinated protein antibodies; DMARD, disease-modifying antirheumaric drugs; MTX, methotrexate; pred, prednisone; SSA, sulphasalazine



Supplementary figure 2: Flowchart of randomization arm 4 (initial combination with methotrexate and infliximab) during year 1 and 2 of follow-up, stratified for ACPA-status.
ACPA, anti-citrullinated protein antibodies; DAS, disease activity score; DMARD, disease-modifying antirheumaric drugs; IFX, infliximab; MTX, methotrexate.

Chapter 7

AGE AFFECTS JOINT SPACE NARROWING IN EARLY ACTIVE RHEUMATOID ARTHRITIS PATIENTS

Gülşah Akdemir*, Xanthe M.E. Matthijssen*, Iris M. Markusse, Theo Stijnen, Nagmeh Riyazi, K. Huub Han, Casper Bijkerk, Pit J.S.M. Kerstens, Willem F. Lems, Tom W.J. Huizinga, Cornelia F. Allaart
*both authors contributed equally

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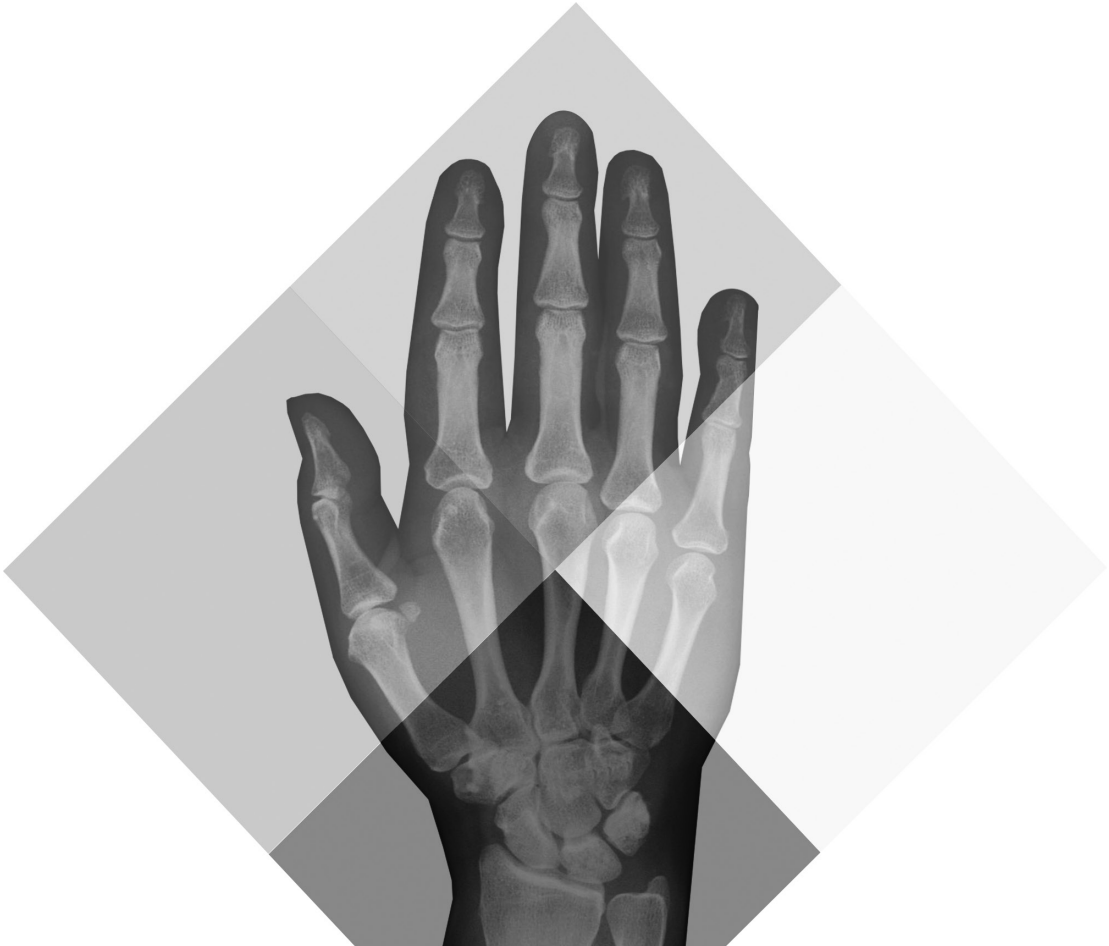

ABSTRACT

Background/purpose

Joint space narrowing (JSN) in rheumatoid arthritis (RA) may be a manifestation of (primary) osteoarthritis becoming more prominent with age. We investigated the severity and predictors of JSN progression among different age-groups.

Methods

Ten year follow-up data of the BeSt study, a randomized controlled treat-to-target trial in early RA were used. Annual X-rays of hands and feet were scored using the Sharp/van der Heijde score (SHS). Subgroups were defined by age at baseline: ≥55, ≥40<55 and <40 years. JSN progression predictors were assessed by Poisson regression.

Results

Baseline JSN scores (median (IQR)) were higher in patients ≥55 (2.0(0.0-6.0)) compared to the other age-groups: 1.0 (0.0-3.0) ≥40<55 and 0.3 (0.0-3.0) <40, p<0.001. After ten years, total JSN and SHS scores were similar in all age-groups.

In patients ≥55 the mean erythrocyte sedimentation rate (ESR) over time (RR 1.02 (95% CI 1.00-1.03)) and the combined presence of rheumatoid factor and anti-citrullinated protein antibodies (RF+/ACPA+) (3.27(1.25-8.53)) were significantly correlated with JSN progression. In patients <40 baseline swollen joint count (SJC) (1.09(1.01-1.18)) and ESR over time (1.04(1.02-1.06)) were significantly associated.

Conclusion

At baseline, RA patients ≥55 years had more JSN than younger patients but after 10 years JSN scores were similar between age-groups. Independent risk factors for JSN progression were baseline SJC and ESR over time in patients <40, RF+/ACPA+ and ESR over time in patients ≥55 years. This suggests that mechanisms leading to JSN progression are related to (residual) rheumatoid inflammation and vary between age-groups. These mechanisms remain to be elucidated.

INTRODUCTION

Joint damage in rheumatoid arthritis (RA) causes progressive disability in patients.[1] Synovial inflammation activates an immune process that causes articular cartilage degradation leading to joint space narrowing (JSN) and excessive local bone resorption and inadequate bone formation resulting in bone erosions.[2,3] Presence and progression of bone erosions and JSN can be scored using plain radiographs of hands and feet using the Sharp/van der Heijde score (SHS).[4] It is well known that joint damage progression is a result of continued high disease activity.[5] Thus, scoring progression of radiographic damage may affect how efficacy of treatment is interpreted, and can influence therapeutic decisions.

However, progression of JSN, and probably to a lesser extend of erosions, may also be a manifestation of primary osteoarthritis (OA) becoming more prominent with increasing age. Lawrence et al showed age-related increases in radiographic OA in both women (prevalence OA of 7.6% in those aged ≥15<24 versus 97% in patients >65) and men (prevalence OA of 9.4% in those aged ≥15<24 versus 97% in patients >65).[6] OA progression seems to be relatively slow but more frequent and more severe OA progression in the distal and proximal interphalangeal joints of older patients was reported previously.[7,8] No definite clinical progression risk factors for radiographic OA progression are known. More painful joints and more self-reported pain appear to increase radiographic OA progression.[9]

Older RA patients show to have a higher baseline damage score. Khanna et al [10] showed that this was mainly due to more joint space narrowing, and this associated with features of hand osteoarthritis. However Mangnus et al showed that the difference between different age-groups could not be fully explained by JSN.[11] Others reported that patients with a higher age at onset were more often anti-citrullinated protein antibodies (ACPA) positive and had more erosions at baseline, and also higher disease activity scores and higher erosion scores during the first two years of treatment.[12,13] Still others showed that in advanced RA, older patients had more JSN than younger patients.[14]

We hypothesized that JSN progression may show a different pattern in older than in younger RA patients. In addition predictors of JSN may be different between these age-groups, due to primary osteoarthritis becoming more prominent with increasing age. We aimed to identify and compare age-specific baseline risk factors for the development of JSN in patients who participated in the BeSt study, a multicenter randomized clinical trial. Early RA patients were treated according to one of four dynamic treatment strategies all aiming a low disease activity (Disease Activity Score: DAS≤2.4). Patients were followed for 10 years and radiographs of hands and feet were obtained annually to score the bone erosions and JSN by the SHS.

PATIENTS AND METHODS

Subjects and design

The BeSt (Dutch acronym for treatment strategies) a multicenter, randomized clinical trial included 508 patients with recent-onset active rheumatoid arthritis (1987 revised American College of Rheumatology criteria [15]) and a symptom duration ≤2 years. All participants gave written informed consent and the medical ethics committee of each participating centre approved the study protocol.

Patients were randomized into four treatment strategies: 1. sequential monotherapy, 2. step-up combination therapy, 3. initial combination therapy with methotrexate, sulfasalazine and prednisone and 4. initial combination therapy with methotrexate and infliximab. Treatment adjustments were made every three months aiming at a DAS <2.4. If DAS was ≤2.4 for six months, treatment could be tapered to maintenance dose, and if then DAS <1.6 was achieved for another six months, medication was discontinued. Once the DAS was ≥1.6 treatment was restarted. Details of the BeSt study have been published elsewhere.[16,17]

Methods of measurement

At baseline, rheumatoid factor (RF) status was evaluated. ACPA status was determined afterwards by the anti-cyclic citrullinated peptide test (anti-CCP2) in available stored baseline serum samples. Health assessment questionnaires (HAQ) [18] and the DAS were assessed at baseline and every three months for ten years. Baseline and annual radiographs, up to 10 years, of hands and feet were collected and were scored, by two independent readers, blinded for patient identity and time order, using the SHS.[4]

Statistical analysis

Median age at baseline in our population was 54.9 years. Based on this median, and considering the unlikelihood of osteoarthritis in patients <40 years old [6] three arbitrary subgroups were created: ‘group <40’ comprising patients aged <40 years, ‘group ≥40<55’ with patients ≥40 years but <55 years and ‘group ≥55’ with patients ≥55 years old at baseline. Baseline characteristics were compared with the multinomial variable ‘age-group’ by the χ^2 test, one-way analysis of variance and Mann-Whitney U test. Pairwise comparisons between the age-groups were performed with the χ^2 test, *t*-test and Kruskall-Wallis test. Mean SHS, Erosion and JSN (progression) scores after 10 years were compared between groups using one-way analysis of variance, with robust standard error estimation and p-values because of the skewed non-normal distributions.

After ten years, DAS and HAQ were known for 292/508 patients, and radiographs were available for 278/508 patients. To avoid bias due to missing data, multiple imputation techniques were performed. The imputed values are based on all radiographs in the study,

and are consequently less sensitive to one measurement error or picture of low quality. To improve resemblance to the normal distribution, annual JSN and erosion scores were log-transformed before imputing. The imputation model incorporated the baseline variables: age, sex, body mass index (BMI), smoking status, randomisation arm, RF status, ACPA status, log-transformed erosion and narrowing score, HAQ score and the components of the DAS. Annual log-transformed erosion and narrowing scores, 10-year HAQ scores and bi-annual DAS were also included in the imputation model.

SHS and JSN scores are always whole non-negative numbers and therefore, JSN progression scores are integers. In our study only 2.2% of the progression scores were negative, hence JSN progression is approximately a count. Furthermore, 37% of the patients had zero JSN progression. For regression modelling of the JSN progression, we used robust Poisson regression after setting the negative progressions to zero. This regression method assumes that the covariates have a multiplicative effect on the mean progression scores, but remains valid if the Poisson is violated. We report the exponentiated regression coefficients, which are interpreted as ratios of means (relative to the reference category for categorical predictors, or corresponding to a one unit increase for numerical predictors). When analyses group were done separately for each age-group we applied Bonferroni correction to adjust for multiple testing.

In the multivariate analysis RF status and ACPA status were coded into one variable because both antibodies are frequently present in the same patients and consequently their influence is confounded by the effect of the other antibody. Since treatment strategy is randomly allocated, it does not confound the effect of other variables and was therefore not included in the multivariate models. All risk factors with a p-value <0.2 were entered in the multivariate models with Bonferroni correction to correct for multiple testing. Accordingly, predictor variables with p-values <0.0167 were considered significant, 98.33% confidence intervals are given, and only predictor variables with univariate p-values <0.066 were entered in the multivariate model. Since we selected our regression variables carefully, we did not remove the determinants from the multivariate analysis when they did not attain significance. Analyses were performed with SPSS 20.0.

RESULTS

Baseline

In the BeSt study, 508 patients were included, 81 (16%) aged <40, 179 (35%) aged ≥40<55 and 248 (49%) aged ≥55. Mean age at baseline was 33, 49 and 66 in the three age-groups, respectively. Table 1 shows the baseline characteristics of the three age-groups.

Table 1: Baseline characteristics in the different age-groups.

	Group <40	Group ≥40<55	Group ≥55	p-value
	n=81	n=179	n=248	
Age. mean ± SD years	33 ± 6	49 ± 5	66 ± 8	
Women. no. (%)	61 (75)	125 (70)	157 (63)	0.10
Smoking. no.(%)	25 (30)	78 (44)	74 (30)	0.01
BMI. mean ± SD	24.4 ± 4.3	26.6 ± 4.5	26.1 ± 3.8	0.001
Time from diagnosis to inclusion. median weeks (IQR)	1.6 (0.7-3.1)	2.4 (1.0-5.3)	2.7 (1.0-4.7)	0.004
Symptom duration. median weeks (IQR)	26.1 (13.4-57.9)	24.6 (15.3-56.1)	22.4 (13.3-44.3)	0.25
RF positive. no. (%)	53 (65)	123 (69)	153 (62)	0.32
ACPA positive no./total no. (%)	43/78 (55)	116/169 (69)	132/226 (58)	0.05
DAS. mean ± SD	4.4 ± 0.9	4.3 ± 0.8	4.5 ± 0.9	0.12
HAQ score. 0-3 scale. mean ± SD	1.3 ± 0.7	1.4 ± 0.6	1.4 ± 0.7	0.49
CRP. mean ± SD	35.4 ± 43.2	32.8 ± 41.9	41.1 ± 43.2	0.14
ESR. mean ± SD	37.1 ± 25.4	34.7 ± 25.7	45.8 ± 28.4	<0.001
Ritchie articular index	14 (9-20)	13 (10-17)	13 (9-18)	0.53
Swollen joint count	14 (10-18)	12 (9-18)	14 (10-19)	0.06
Total SHS. 0-448 scale				
median (IQR)	1.0 (0.0-3.0)	1.0 (0.0-4.5)	2.5 (1.0-7.4)	<0.001
mean ± SD	2.4 ± 3.7	3.1 ± 4.9	5.0 ± 6.8	
Erosion score. 0-280 scale				
median (IQR)	0.0 (0.0-0.3)	1.0 (0.0-3.0)	0.0 (0.0-1.0)	<0.001
mean ± SD	0.5 ± 1.4	0.9 ± 2.6	1.1 ± 2.0	
JSN score. 0-168 scale				
median (IQR)	0.3 (0.0-3.0)	1.0 (0.0-3.0)	2.0 (0.0-6.0)	<0.001
mean ± SD	1.9 ± 2.9	2.2 ± 3.2	3.9 ± 5.5	
Treatment strategy				
Sequential monotherapy, no. (%)	19 (24)	51 (29)	56 (23)	0.52
Step-up therapy, no. (%)	18 (22)	47 (26)	56 (23)	
Initial combination therapy with prednisone, no. (%)	22 (27)	45 (25)	66 (27)	
Initial combination therapy with infliximab, no. (%)	22 (27)	36 (20)	70 (28)	

RF: rheumatoid factor, ACPA: Anti–citrullinated protein antibodies, DAS: disease activity score, HAQ: health assessment questionnaire, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, SHS: Sharp/van der Heijde score, JSN: joint space narrowing, SD: standard deviation, IQR: interquartile range.

The variables that were statistically significantly associated with the multinomial variable 'age-group' (<40, ≥40<55 and ≥55), showed statistically significant differences when compared pairwise between age-groups. 30%, 44% and 30% of the three age-groups participants were noted as 'smokers' at baseline (group ≥40<55 vs. group ≥55, p=0.004). Mean BMI was 24.4 in group <40, 26.6 in group ≥40<55 (group <40 vs. group ≥40<55, p<0.001) and in 26.1 in group

≥55 (group <40 vs. group ≥55, p=0.001). Erythrocyte sedimentation rate (ESR) was higher in group ≥55 compared to group <40 (mean 46 vs. 37 ; p=0.01) and group ≥40<55 (mean 46 vs. 35; p<0.001). Time from diagnosis was lower in group <40 compared to group ≥40<55 and group ≥55 (p=0.002 and p=0.004 respectively).

Pairwise age-group comparison of the variables not statistically significantly associated with 'age-group' was performed, but showed no statistically significant differences between groups except for DAS and swollen joint count (SJC) (data not shown). Age-group <40 had similar baseline DAS and SJC compared to groups ≥40<55 and ≥55. Group ≥40<55 had lower DAS compared to group ≥55 (4.3 vs. 4.5; p=0.04) and a lower baseline SJC compared to group ≥55 (median (interquartile range IQR) (12 (9-18) vs. 14 (10-19); p=0.02)). More patients were ACPA positive in group ≥40<55 than in group <40 (68% vs. 55%; p=0.05) and group ≥55 (68% vs 58%; p=0.05). Both ACPA and RF were present in 46%, 60% and 48% of the patients in group <40, group ≥40<55 and group ≥55, respectively.

All baseline radiographic scores were similar in group <40 and group ≥40<55. Baseline SHS score was higher in group ≥55 (median 2.5, IQR 1.0-7.4) compared to the other groups (group <40: 1.0 (0.0-3.0); group ≥40<55: 1.0 (0.0-4.5; p<0.001). Baseline erosion scores were higher in group ≥55 compared to group ≥40<55 (1.0 (0.0-3.0) vs. 0.0 (0.0-1.0); p=0.006) and group <40 (0.0 (0.0-0.3); p<0.001). Also, more patients in group ≥55 had JSN ≥0.5 (70% vs 50% in group <40; p=0.001; and 55% in group ≥40<55; p=0.002) and the median JSN score was higher compared to the other groups (2.0 (0.0-6.0) in group ≥55 vs. 0.3 (0.0-3.0) in group <40 and 1.0 (0.0-3.0) in group ≥40<55; p<0.001). JSN in the proximal interphalangeal joints increased with age: (mean ± SD) 0.1 ± 0.5 (median (IQR) 0.0 (0.0-0.0)) in group <40, 0.2 ± 0.5 (0.0 (0.0-0.0)) in group ≥40<55 and 0.4 ± 0.9 (0.0 (0.0-0.5)) group ≥55 (<40 vs. ≥40<55 p=0.06; <40 vs. ≥55 p=0.001; ≥40<55 vs. ≥55 p= 0.02). This trend was not observed in the metacarpophalangeal joints. JSN scores in metacarpophalangeal joints are higher in group ≥55 compared to group ≥40<55 (0.6 ± 1.2 (0.0 (0.0-1.0)) vs. 0.4 ± 0.9 (0.0 (0.0-0.0)), p=0.01) but not compared to group <40 (0.5 ± 0.9 (0.0 (0.0-1.0)); <40 vs. ≥55 p=0.51)

Outcomes after ten years

Ten-year follow-up characteristics are shown in table 2. Average DAS over time was similar in all groups. ESR over time was higher in group ≥55 (mean 22) compared to the other groups (mean 17 <40 and mean 18 in group ≥40<55; p=0.01 group <40 vs. ≥55, p<0.01 group ≥40<55 vs. ≥55). After ten years of follow-up none of the mean radiographic scores differed between the age-groups but JSN ≥ 0.5 was found more often in group ≥55 (90%) compared to group <40 (75%) and in group ≥40<55 (80%) (p=0.001 and p=0.008, respectively).

Table 2: Outcomes 10 years after randomisation

	Group <40	Group ≥40<55	Group ≥55	p-value <40 vs ≥40<55	p-value <40 vs ≥55	p-value ≥40<55 vs ≥55
	n=81	n=179	n=248			
DAS over time. mean ± SD	2.0 ± 0.7	2.0 ± 0.6	2.1 ± 0.6	0.68	0.57	0.18
ESR over time. mean ± SD	17.2 ± 12.3	17.8 ± 11.6	22.1 ± 16.1	0.73	0.01	<0.01
Total SHS. 0-448 scale						
median (IQR)	4.1 (1.2-12.5)	6.5 (2.0-15.5)	7.0 (3.0-15.5)	0.69	0.57	0.75
mean ± SD	15.0 ± 32.4	13.5 ± 20.3	12.9 ± 17.1			
SHS progression						
median (IQR)	2.7 (0.0-7.0)	3.0 (0.5-11.7)	2.5 (0.5-8.4)	0.54	0.19	0.15
mean ± SD	12.6 ± 31.0	10.4 ± 18.5	7.8 ± 15.9			
Erosion score. 0-280 scale						
median (IQR)	1.0 (0.0-3.8)	1.3 (0.3-5.0)	1.5 (0.5-4.0)	0.91	0.37	0.07
mean ± SD	4.9 ± 13.0	5.1 ± 9.6	3.6 ± 6.5			
Erosion progression						
median (IQR)	0.8 (0.0-3.0)	1.0 (0.0-4.0)	0.8 (0.0-2.1)	0.93	0.20	0.02
mean ± SD	4.3 ± 12.7	4.2 ± 8.1	2.5 ± 6.2			
JSN score. 0-168 scale						
median (IQR)	3.0 (0.5-8.0)	4.0 (1.0-10.0)	5.3 (2.0-11.5)	0.48	0.73	0.47
mean ± SD	10.1 ± 20.4	8.4 ± 12.4	9.4 ± 12.0			
JSN progression						
median (IQR)	1.0 (0.0-5.0)	1.9 (0.0-7.5)	1.8 (0.0-5.5)	0.36	0.20	0.49
mean ± SD	8.2 ± 19.3	6.2 ± 11.6	5.4 ± 11.2			

DAS: disease activity score. ESR: erythrocyte sedimentation rate. SHS: Sharp/van der Heijde score. JSN: joint space narrowing. SD: standard deviation. IQR: interquartile range.

SHS progression was similar in all groups (2.7 (0.0-7.0); 3.0 (0.5-11.7); 2.5 (0.5-8.4)). Erosion progression scores were higher in group ≥40<55 compared to group ≥55 (1.0 (0.0-4.0) vs. 0.8 (0.0-2.1); p=0.02). JSN progression did not differ statistically significantly between the age-groups: (mean ± SD) 8.2±19.3 (median (IQR) 1.0 (0.0-5.0)) in group <40, 6.2±11.6 (1.9 (0.0-7.5)) in group ≥40<55 and 5.4±11.2 (1.8 (0.0-5.5)) in group ≥55. Scores at ten-year and progression scores are shown in figure 1. While the median progression scores are higher in the oldest groups, JSN progression scores are more skewed to the right (higher progression scores) in the youngest group, as reflected by a higher mean and higher standard deviation in that group.

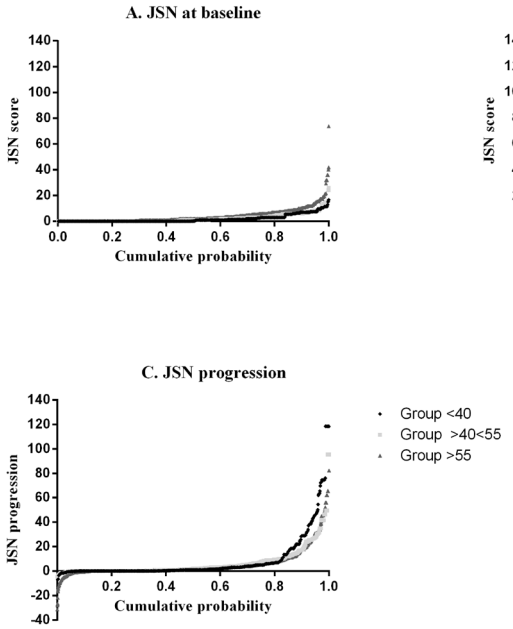

Figure 1 Probability plots JSN score at baseline (A), ten years (B) and progression (C) for the different age-groups (Darkest dots: group <40, lightest dots group ≥40<55, intermediate dots: group ≥55)
JSN: joint space narrowing.

Predictive factors for JSN progression

Univariate risk factors that were statistically significantly associated with JSN progression in group <40 were JSN at baseline (RR (IQR)) (1.17 (1.01-1.35)), baseline SJC (1.11 (1.02-1.21)), ACPA+ (3.79 (1.21-11.89)), RF+/ACPA+ (5.39 (1.25-23.15)) and average ESR over time (1.04 (1.00-1.08)) (table 3) and initial combination therapy with infliximab was protective against JSN progression compared to sequential monotherapy (0.20 (0.04-0.95)). In group

≥40<55, erosions at baseline (1.06 (1.01-1.12)), RF+ (2.88 (1.40-5.96)), RF+/ACPA+ (3.41 (1.33-8.71)) and average ESR (1.02 (1.00-1.04)) were correlated with JSN progression. Also, initial combination therapy with infliximab (0.49 (0.19-1.27)) compared to sequential monotherapy tended to protect against JSN progression in group ≥40<55. In group ≥55, smoking (2.00 (1.11-3.58)), RF+ (2.63 (1.31-5.28)), ACPA+ (3.39 (1.58-7.28)), RF+/ACPA+ (4.19 (1.58-11.07)) and average ESR (1.02 (1.01-1.03) were statistically significantly related to JSN progression. Treatment strategies were not correlated with JSN progression in group ≥55.

Table 3: Univariate Poisson regression analysis per age-group

	Group <40		**Group ≥40<55**		**Group ≥55**	
	RR	**95% C.I.**	**RR**	**95% C.I.**	**RR**	**95% C.I.**
Baseline						
smoking	0.83	(0.16-4.23)	1.18	(0.60-2.32)	2.00	(1.11-3.58)
BMI<25	Ref		Ref		Ref	
BMI>25<30	0.91	(0.22-3.82)	0.58	(0.37-1.50)	1.12	(0.58-2.14)
BMI>30	0.28	(0.05-1.66)	0.74	(0.19-1.73)	1.19	(0.50-2.87)
Ritchie articular index	1.00	(0.94-1.06)	0.95	(0.89-1.01)	0.98	(0.93-1.03)
Swollen joint count	**1.11**	**(1.02-1.21)**	0.97	(0.93-1.01)	1.01	(0.98-1.05)
JSN	**1.17**	**(1.01-1.35)**	1.06	(0.99-1.14)	1.00	(0.94-1.07)
Erosions	1.13	(0.90-1.41)	**1.06**	**(1.01-1.12)**	1.02	(0.89-1.15)
RF-/ACPA-	Ref		Ref		Ref	
RF+/ACPA-	1.65	(0.28-9.82)	3.31	(0.93-11.75)	1.47	(0.48-4.47)
RF-/ACPA+	2.78	(0.48-16.15)	1.76	(0.54-5.79)	2.52	(0.84-7.54)
RF+/ACPA+	**5.39**	**(1.25-23.15)**	**3.41**	**(1.33-8.71)**	4.19	(1.58-11.07)
RF-	Ref		Ref		Ref	
RF+	2.81	(0.90-8.77)	**2.88**	**(1.40-5.96)**	2.63	(1.31-5.28)
ACPA-	Ref		Ref		Ref	
ACPA+	**3.79**	**(1.21-11.89)**	2.02	(0.94-4.33)	3.39	(1.58-7.28)
Average ESR over time	1.04	(1.00-1.08)	**1.02**	**(1.00-1.04)**	1.02	(1.01-1.03)
Sequential monotherapy	Ref		Ref		Ref	
Step up to combination therapy	0.44	(0.07-2.79)	1.29	(0.56-3.02)	0.81	(0.34-1.93)
Initial combination therapy with prednisone	0.89	(0.20-3.93)	0.77	(0.36-1.64)	0.93	(0.38-2.25)
Initial combination therapy with infliximab	**0.20**	**(0.04-0.95)**	0.49	(0.19-1.27)	0.84	(0.36-2.00)

BMI: body mass index, JSN: joint space narrowing, RF: rheumatoid factor, ACPA: Anti–citrullinated protein antibodies, ESR: erythrocyte sedimentation rate; Erosions: erosion score (SHS); RR.: relative risk, 95% C.I.: 98.33% (Bonferroni correction) confidence interval.

Risk factors with a p-value <0.067 were entered in the multivariate analysis per age-group (table 4). In the multivariate Poisson regression, in group <40 baseline SJC (1.09 (1.01-1.18)) and average ESR (1.04 (1.02-1.06)) were independently associated with JSN progression. In group ≥40<55 none of the risk factors were significantly correlated, but the influence of the combined presence of RF and ACPA showed a trend (4.00 (0.88-18.10)). In group ≥55 ten-

year average ESR (1.02 (1.00-1.03)) and the combined presence of RF and ACPA (3.27 (1.25-8.53)) were significantly associated with JSN progression. If only baseline variables were incorporated in the multivariate model, similar results were yielded, however the influence of the combined presence of RF and ACPA in group ≥40<55 attained significance. (data not shown).

Table 4: Multivariate Poisson regression analysis per age-group

Group <40	**RR**	**95% C.I.**
Baseline JSN	1.07	(0.95-1.22)
Swollen joint count	**1.09**	**(1.01-1.18)**
RF- /ACPA-	Ref	
RF+ /ACPA-	1.80	(0.29-11.25)
RF- /ACPA+	3.14	(0.34-28.66)
RF+/ACPA+	4.00	(0.88-18.08)
Time average ESR	**1.04**	**(1.02-1.06)**
Group ≥40<55	**RR**	**95% C.I.**
Baseline JSN	1.02	(0.95-1.10)
Baseline Erosions	1.04	(0.98-1.10)
Ritchie articular index	0.96	(0.89-1.03)
Swollen joint count	1.00	(0.95-1.10)
RF- /ACPA-	Ref	
RF+ /ACPA-	2.67	(0.76-9.39)
RF- /ACPA+	1.28	(0.37-4.43)
RF+/ACPA+	2.65	(0.95-7.38)
Time average ESR	1.01	(0.99-1.04)
Group ≥55	**RR**	**95% C.I.**
Smoking at baseline	1.46	(0.81-2.63)
RF- /ACPA-	Ref	
RF+ /ACPA-	1.33	(0.45-3.98)
RF- /ACPA+	2.31	(0.75-7.10)
RF+/ACPA+	**3.27**	**(1.25-8.53)**
Time average ESR	**1.02**	**(1.00-1.03)**

RF: rheumatoid factor; ACPA: anti-citrullinated protein antibodies; ESR: erythrocyte sedimentation rate; JSN: joint space narrowing; RR: relative risk; 95% C.I.: 95% confidence interval after Bonferroni correction.

DISCUSSION

Radiographic damage progression, as potential cause of permanent disability, is an important target for preventive therapy and one of the main determinants of successful treatment in patients with rheumatoid arthritis. However, in some RA patients primary osteoarthritis (OA), represented by joint space narrowing may contribute to radiographic joint damage progression. Previous cross sectional studies [10-12,14] have shown that older RA patients had higher damage

scores than younger RA patients at baseline, partly explained by higher JSN [10,11] In addition radiographic OA is more often present in older patients and progression is more frequent and more severe in older patients. Risk factors for OA progression differ from risk factors for RA progression.[6-8]
We hypothesized that older RA patients also show more JSN progression over time than younger patients, because progression in JSN is caused by both RA and OA, and that progression of JSN was associated with different risk factors in different age-groups.
To investigate our hypothesis, we compared the severity of JSN between the age-groups and tried to identify age-group-specific risk factors in a cohort of patients with recent onset RA (1987 criteria), who were treated to target DAS≤2.4 over the course of 10 years, with three-monthly DAS calculation and treatment adjustments, and radiographs of hands and feet taken at baseline and yearly thereafter. JSN scores were derived from the Sharp/van der Heijde score.

As expected, we found that RA patients of ≥55 years old showed JSN more often and more severe JSN at baseline than younger patients. It was shown that while damage to the proximal interphalangeal joints at baseline increases with age, damage to the metacarpophalangeal joints does not. Older patients had higher ESR, higher SJC, higher DAS and a higher baseline erosion score suggesting that in older patients there was more rheumatoid inflammation. After 10 years, there were no statistically significant differences between the age-groups in the amount of JSN progression, but JSN progression was more skewed to the right in the youngest group, as reflected by a higher mean and higher standard deviation in that group. Risk factors for JSN progression were only slightly different in the three age-groups. In patients ≥55 years, presence of RF and ACPA and a high ESR as marker for systemic inflammation over time were independent risk factors for JSN progression. Also in patients <40 years, high inflammatory activity, represented by baseline SJC and ESR over time, was independently associated with JSN progression, but presence of auto-antibodies was not. In the >40 ≤55 years age-group there were no independent predictors for JSN progression.
These results confirm previous reports that JSN is more prevalent and more severe in older RA patients than in younger patients at baseline. However, contrary to our hypothesis, we did not find more JSN progression in older patients. In fact, the most severe JSN progression was observed in (a subgroup of) patients <40 years. Slow progression observed in (a subgroup of) older patients may in part represent JSN due to primary osteoarthritis, which has been shown to be slowly progressive and more prevalent in older patients.[7,8,19]
This hypothesis is supported by the fact that, although ESR over time was higher in the oldest group than in the other age-groups, as is observed in healthy individuals,[20] DAS over time was not, indicating that the swollen joint counts and Ritchie Articular Index results over time were low.

RA appears to have been well suppressed in the older patients, which is also suggested by the finding that the mean erosion progression score was lower than in the other age-groups. Primary osteoarthritis is supposed to be relatively rare in the ≤40 years age-group, but over 10 years follow up may have progressively occurred, adding to the increased JSN progression scores due to inflammation in those patients. However, in the younger patients erosion progression scores were also higher, suggesting that from baseline, when they had a higher SJC, over 10 years follow up, when they had similar DAS but lower ESR, RA may have been insufficiently suppressed. That initial combination therapy in the older patients is not associated with less JSN progression may suggest that JSN progression in older patients is caused by osteoarthritis which is less susceptible to the treatment with TNF-inhibitors.[21] However, in older patients, combined presence of RF and ACPA was associated with more damage progression. In general, these antibodies have been associated with a more destructive disease course in RA. A previous analysis of the BeSt study [22] showed that presence of ACPA did not affect the suppression of inflammation, but even in patients with similar low disease activity was associated with more damage progression. Why this is not found for younger patients in this study remains to be investigated, but might be explained by the smaller sample size in the age-group <40.

Previous studies have looked at the possible contribution of primary osteoarthritis to JSN scores in RA patients [14,23,24] by multivariate linear analysis adjusted for age. This statistical method assumes a linearity of the relationship between age and outcome that may not exist in the oldest patients [25] and does not take into account the non-linear interaction between some risk factors and age. By stratifying into different age-groups, we could assess non-linear relations between age and risk-factors. The downside of our method is a loss of power and the loss of differentiation between ages that belong in one age-group. The age limits per group were set arbitrarily, in part based on the median age in the total group (55 years), the need for sufficient numbers of patients per group and the presumption that significant primary osteoarthritis is unlikely in patients under 40 years old. We were able to follow patients for 10 years, whereas previous studies had shorter follow up periods. During these 10 years all patients received treatment targeted at a Disease Activity Score ≤2.4. This resulted, as previous analyses [26] have shown, in similarly well controlled rheumatoid disease activity in all patients in the four strategy arms from 1 year on.

It can be argued that to distinguish primary osteoarthritis from rheumatoid joint damage, one of the specific scoring methods for osteoarthritis should have been used.[19] These however may also include rheumatoid joint damage in the score, and it remains unclear which is the best method to score osteoarthritis progression. Instead, we looked at joint space narrowing as part of the Sharp/van der Heijde score (SHS), precisely to highlight that a method to measure outcomes of RA treatment can be susceptible to overestimation of rheumatoid damage by including osteoarthritis. Our hypothesis that JSN in older patients is caused by both RA and

OA was supported by increasing JSN at baseline in the proximal interphalangeal joints but not in the metacarpophalangeal joints. However, the potentially combined presence of rheumatoid damage and osteoarthritic features suggest that risk factors identified in our analyses might also be risk factors for both causes of JSN progression.

In conclusion, in different age-groups of patients with rheumatoid arthritis, joint space narrowing scores and progression of joint space narrowing may be influenced by various factors, one of which may be primary osteoarthritis in the older age-groups. This may affect how radiographic scoring methods can be interpreted to represent treatment effects of anti-rheumatic therapy in different age-groups. In all patients, inflammation should be optimally suppressed to avoid progression of joint damage which may determine long term functional ability. At baseline disease seems to be more severe in older persons, but after 10 years, radiographic outcomes do not differ between age-groups, implicating that progression in the younger patients might not be optimally suppressed. Finally, a possible association between inflammation and progression of osteoarthritis should be further investigated by including specific osteoarthritis scoring methods and by evaluation in other cohorts, as this knowledge may open a door to preventive treatment.

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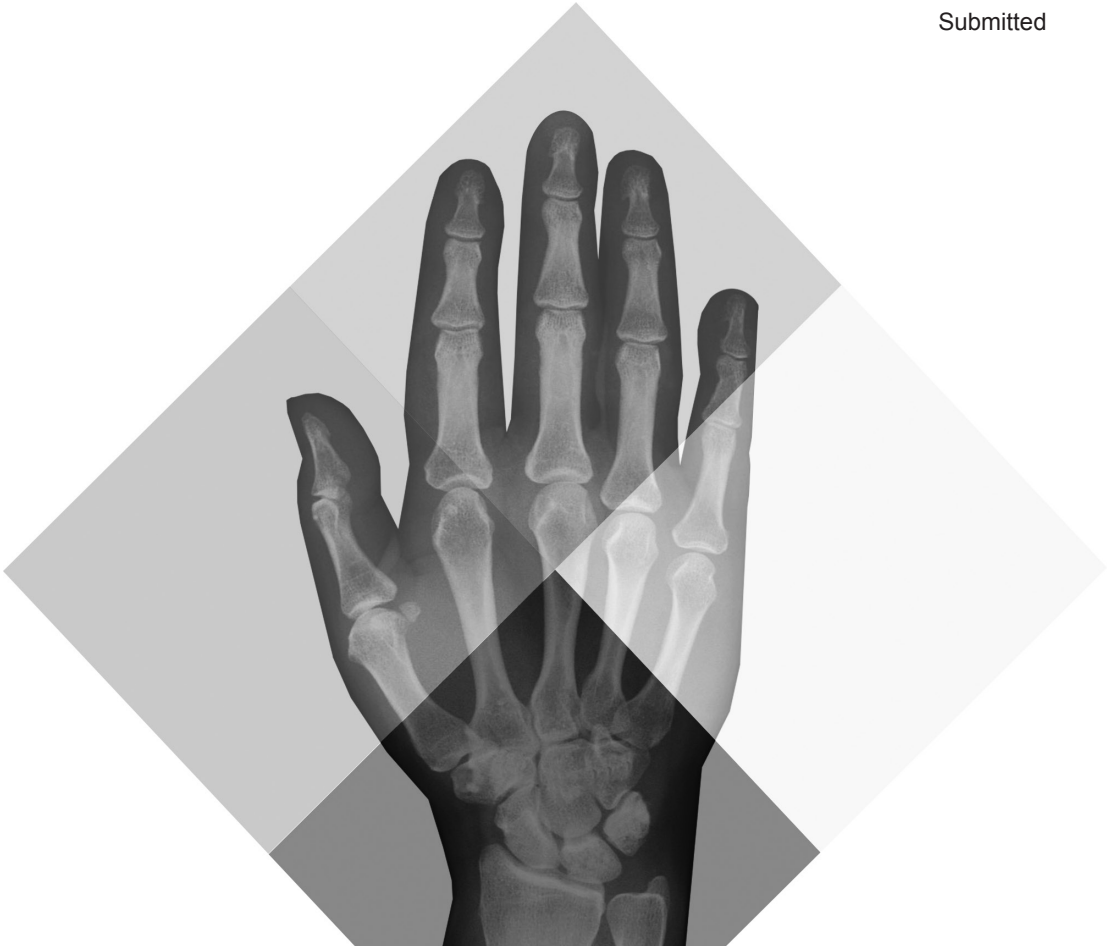
Chapter 8

A COMPARISON BETWEEN LOW DISEASE ACTIVITY OR DAS-REMISSION AS TREATMENT TARGET IN EARLY ACTIVE RHEUMATOID ARTHRITIS PATIENTS

Gülşah Akdemir, Iris M. Markusse, Sytske Anne Bergstra, Robbert J. Goekoop, Esmeralda T. Molenaar, Johannes H.L.M. van Groenendael, Pit J.S.M. Kerstens, Willem F. Lems, Tom W.J. Huizinga, Cornelia F. Allaart

Submitted



ABSTRACT

Objective

To assess which treatment target (low disease activity or disease activity score (DAS)-remission) is associated with better outcomes in DAS-steered treatment in early active rheumatoid arthritis (RA) patients.

Methods

Five years outcomes were compared in 133 early active RA (1987) patients, randomized to initial therapy with methotrexate, sulfasalazine and tapered high dose of prednisone, targeted at DAS≤2.4 (BeSt-study), and 175 early RA patients (IMPROVED-study) who would have fulfilled inclusion criteria of the BeSt-study, starting methotrexate and tapered high dose of prednisone, targeted at DAS<1.6. Association of treatment target with DAS<1.6, Boolean remission at year 1 and drug-free DAS-remission (DFR) at year 5 were analysed by logistic regression analysis.

Results

At baseline, DAS<1.6 steered patients had a milder disease (mean DAS 4.1±0.7 vs 4.4±0.9, p=0.012) than DAS≤2.4 steered patients and less radiological damage. DAS decreased similarly over time and functional ability was similar in both patient groups. Radiological damage progression over time was similar in both patient groups. DAS≤2.4 was achieved in similar percentages in both patient groups, but more DAS<1.6 steered patients achieved DAS<1.6 and DFR. DAS<1.6 steered group was associated with DAS<1.6 (OR 3.04 (95% CI 1.64-5.62)) and Boolean remission (3.03 (1.45-6.33)) at year 1 and DFR at year 5 (3.77 (1.51-9.43)) corrected for symptom duration, baseline DAS, baseline SHS, time on anti-TNF and gender.

Conclusion

DAS<1.6 steered treatment results in better outcomes than DAS≤2.4 steered treatment in early active RA patients and is associated with DAS<1.6 and Boolean remission at year 1 and DFR at year 5.

INTRODUCTION

Initial combination therapy followed by targeted therapy is the optimal treatment strategy to suppress disease activity in early arthritis patients.[1-6] Treat-to-target therapy has been introduced in clinical trials and implemented in daily practice. The optimal treatment target is under discussion, and head to head comparisons are lacking. International recommendations state that treatment should be steered at achieving remission (Disease Activity Score (DAS)<1.6) or at least low disease activity (DAS<2.4).[7] Instinctively, remission appears the optimal treatment target, as this is associated with better functional ability and less damage progression.[4;6] However, this association may not be a causal relationship. To proceed with further treatment adjustments aiming at remission when low disease activity is achieved may not bring additional clinical benefits, but additional costs and risks for side effects.
We aimed to investigate which treatment target, low disease activity or DAS-remission, is more effective in early rheumatoid arthritis (RA) patients by comparing two treat-to-target studies: the BeSt-study, a randomized clinical trial, aiming at DAS≤2.4 and the IMPROVED-study, a two-step randomized clinical trial, aiming at DAS<1.6. We compared clinical outcomes during 5 years of BeSt patients in arm 3 (initial combination therapy with prednisone), to IMPROVED patients (starting induction therapy) who would have fulfilled the inclusion criteria of the BeSt-study.

PATIENTS AND METHODS

Study design and patients

The Behandel Strategieën (Treatment Strategies for Rheumatoid Arthritis) (BeSt)-study (NTR262, NTR 265 (Dutch trial registry)) was a multicenter, randomized, clinical trial and introduced treat-to-target therapy in the year 2000 in 20 hospitals in the Netherlands. Five-hundred-and-eight patients with early (≤2 years symptom duration) active (≥6 of 66 swollen joints, ≥6 of 68 tender joints, and either erythrocyte sedimentation rate (ESR) ≥28 mm/hour or a visual analogue scale (VAS) global health score ≥20mm) [3] RA (American College of Rheumatology (ACR) 1987 classification criteria)(8) were randomized to 4 treatment strategies, 3-monthly aiming at low disease activity (DAS≤2.4). Treatment was intensified as long as DAS>2.4, but tapered when DAS was ≤2.4 for at least 6 consecutive months. From year 3, patients who had tapered to low dose single disease modifying antirheumatic drug (DMARD) and were in DAS-remission (DAS<1.6) for at least 6 consecutive months, stopped treatment to achieve drug-free DAS-remission (DFR). For the current study, 133 patients randomized to arm 3, initially treated with methotrexate (MTX) 7.5mg/week, sulfasalazine (SSZ) 2000mg/day and a tapered high dose of prednisone (tapered in 7 weeks from 60mg/

day to 7.5mg/day) were selected. If after 3 months DAS remained >2.4, MTX was increased to 25 mg/week. Further treatment adjustments are shown in supplementary figure 1. These patients will be called the 'DAS≤2.4 steered group'.

The Induction therapy with MTX and Prednisone in Rheumatoid Or Very Early arthritic (Disease (IMPROVED)-study ISRCTN Register number 11916566 and EudraCT number 2006 06186-16) was a multicenter, randomized, clinical trial that started in 2007 in most of the hospitals that also participated in the BeSt-study. Six-hundred-and-ten patients with early (≤2 years symptom duration) RA according to the 2010 ACR and European League Against Rheumatism (EULAR) classification criteria [9] or undifferentiated arthritis, all received initial treatment with MTX 25mg/week and a tapered high dose of prednisone (tapered from 60mg/day to 7.5mg/day in 7 weeks) for 4 months,[6] with 4-monthly treatment options aiming at DAS-remission (<1.6).[10] Patients who achieved early DAS-remission at 4 months tapered and stopped prednisone, followed by MTX if DAS-remission persisted at 8 months (supplementary figure 2). DFR could be achieved no sooner than at year 1. Patients who did not achieve DAS-remission at 4 months were randomized to arm 1 (MTX 25mg/week, prednisone 7.5mg/day, SSZ 2000mg/day and hydroxychloroquine 400mg/day) or arm 2 (MTX 25mg/week and adalimumab 40mg/2 weeks).[4] For the current analysis, 175 RA (1987) patients who fulfilled the inclusion criteria of the BeSt-study were selected. These patients will be called the 'DAS<1.6 steered group'.

Approval for the BeSt-study and the IMPROVED-study was given by the Medical Ethics Committee of each participating center and all patients gave written informed consent. LUMC Medical Ethics Committee approval number for the BeSt-study was P02.189 and for the IMPROVED-study was P06.210. More details of the BeSt-study and the IMPROVED-study were published elsewhere.[3-6]

ACR/EULAR (Boolean) remission [11] was defined by tender joint count (TJC) ≤1, swollen joint count (SJC) ≤1, C-reactive protein (mg/dl) ≤1 and VAS global health (0-10 scale) ≤1.

Baseline and annual radiographs of hands and feet were scored using the Sharp/van der Heijde score (SHS [12]) in each study by 2 independent readers blinded for patient identity and allocation. The BeSt-study was scored in random order and the IMPROVED-study in chronological order. For the analysis the means of the 2 readers for each study (IM & GA BeSt-study and GA & SB IMPROVED-study) were used to compare SHS and progression. Progression was defined by ≥0.5 point increase after 1 and 5 years.

Statistical analyses

Outcomes were analyzed by student *t*-tests, Mann-Whitney U tests and Chi-squared tests. DAS, delta DAS, functional ability assessed by the Dutch Health Assessment Questionnaire (HAQ [13]), low disease activity percentages, DAS-remission percentages, and DFR percentages were compared at year 1 and year 5. Association of treatment target (DAS≤2.4 or DAS<1.6)

with DAS<1.6, Boolean remission at year 1 and (DFR) at year 5 were analysed by logistic regression analysis. The multivariable model was corrected for baseline differences (DAS, symptom duration, total SHS) between the studies, time on anti-tumour necrosis factor (TNF) inhibitor and other variables from the literature. Statistical analyses were performed with SPSS for Windows version 23.0.

RESULTS

Study population

At baseline the patients had a similar mean age and percentages of females in the studies were similar (table 1). Patients in the DAS<1.6 steered group had a significantly shorter symptom duration (median 17 (IQR 8-28) weeks vs 23 (15-53) (DAS≤2.4), p<0.001) and lower DAS (mean 4.1±SD 0.7 vs. 4.4±0.9, p=0.012) compared to the DAS≤2.4 steered group. This was due to a lower TJC and lower SJC in the DAS<1.6 steered group, whereas ESR were comparable. VAS global health was statistically higher in the DAS<1.6 steered group. Functional ability was comparable in both studies. The proportions of patients with rheumatoid factor (RF) positivity and anti-citrullinated protein antibodies (ACPA) positivity were similar in both groups. SHS at baseline was significantly higher in the DAS≤2.4 steered group compared to the DAS<1.6 steered group (median (IQR)/mean±SD 1.5 (0-3)/2.8±3.8 vs. 0 (0-3)/1.8±2.9, p=0004).

Early response

After 3 months in the DAS≤2.4 steered group, the DAS was decreased by 2 points to 2.4±1.0 and HAQ to 0.6±0.6 (table 1 and figure 1A and 3B). The target of DAS≤2.4 was achieved by 75/133 (56%) of the patients and 27/133 (20%) were in DAS-remission (table 1 and figure 1C). In the DAS<1.6 steered group at 4 months, DAS had decreased by mean 2.4 points to 1.8±1.0 and HAQ to 0.5±0.6 (table 1 and figure 1A and 3B). The target of DAS-remission was achieved by 92/175 (53%) of the patients (table 1 and figure 1C). Patients in DAS-remission started tapering medication, while 64 patients (37%) not in DAS-remission at 4 months were randomized: 30 patients to arm 1 and 34 patients to arm 2. Of these, 25/64 (39%) had DAS≤2.4. Seventeen patients (10%) who did not achieve early DAS-remission were not randomized, and were treated outside of protocol. At 4 months 126/175 (72%) had DAS≤2.4. There were 2 patients who left the study before the evaluation at 4 months.

Table 1: Clinical characteristics at baseline and follow up in DAS≤2.4 steered (BeSt) and DAS<1.6 steered (IMPROVED) patients

Baseline	BeSt n=133	IMPROVED n=175	p-value
Age (years), mean ± SD	55 ± 14	53 ± 15	0.408
Female, n (%)	88 (66)	126 (72)	0.271
Symptom duration (weeks), median (IQR)	23 (15-53)	17 (8-28)	<0.001
DAS, mean ± SD	4.4 ± 0.9	4.1 ± 0.7	0.012
Tender joint count, median (IQR)	13 (9-19)	10 (8-14)	<0.001
Swollen joint count, median (IQR)	14 (10-18)	11 (8-17)	0.023
ESR mm/h, median (IQR)	35 (17-46)	32 (17-52)	0.761
VAS general health, mean ± SD	51 ± 22	57 ± 22	0.010
HAQ, mean ± SD	1.4 ± 0.7	1.5 ± 0.6	0.114
RF positive, n (%)	86 (65)	108 (62)	0.999
ACPA positive, n (%)	68 (51)	98 (56)	0.715
Total SHS, median (IQR)/mean ± SD	1.5 (0-3)/2.8±3.8	0 (0-3)/1.8±2.9	0.004
3 months (BeSt) or 4 months (IMPROVED)			
DAS, mean ± SD	2.4 ± 1.0	1.8 ± 1.0	
∆ DAS, mean ± SD	2.0 ± 1.1	2.4 ± 1.1	
Tender joint count, median (IQR)	5 (2-8)	2 (0-5)	
Swollen joint count, median (IQR)	3 (1-8)	0 (0-2)	
ESR mm/h, median (IQR)	8 (4-17)	10 (5-17)	
VAS general health, mean ± SD	28 ± 22	23 ± 20	
HAQ, mean ± SD	0.6 ± 0.6	0.5 ± 0.6	
DAS>2.4, n (%)	56 (42)	46 (26)	
DAS≥1.6 - ≤2.4, n (%)	48 (36)	34 (19)	
DAS-remission, n (%)	27 (20)	92 (53)	
1 year			
DAS, mean ± SD	2.0 ± 0.9	1.6 ± 1.0	0.004
∆ DAS, mean ± SD	2.4 ±1.1	2.5 ± 1.1	0.445
Tender joint count, median (IQR)	4 (1-6)	2 (0-4)	<0.001
Swollen joint count, median (IQR)	1 (0-3)	0 (0-2)	0.002
ESR mm/h, median (IQR)	9 (5-15)	9 (5-18)	0.900
VAS general health, mean ± SD	27 ± 23	24 ± 22	0.274
HAQ, mean ± SD	0.5 ± 0.5	0.6 ± 0.6	0.148
DAS>2.4, n (%)	33 (25)	36 (21)	0.333
DAS≥1.6 - ≤2.4, n (%)	49 (37)	38 (22)	0.002
DAS-remission, n (%)	40 (30)	89 (51)	<0.001
Drug-free DAS-remission, n (%)	Not allowed	27 (15)	
ACR/EULAR Boolean remission, n (%)	21 (16)	46 (26)	0.004
SHS progression, year 0-1, median (IQR)/mean ± SD	0 (0-1)/0.9±2.3	0 (0-0)/0.4±1.6	0.164
5 years			
DAS, mean ± SD	1.7 ± 0.8	1.5 ± 0.8	0.014
∆ DAS, mean ± SD	2.6 ± 1.1	2.7 ±1.0	0.849
Tender joint count, median (IQR)	2 (0-4)	1 (0-2)	0.013
Swollen joint count, median (IQR)	0 (0-3)	0 (0-1)	<0.001
ESR mm/h, median (IQR)	11 (6.3-18.8)	11 (6-18.3)	0.917
VAS general health, mean ± SD	27 ± 22	24 ± 21	0.216
HAQ, mean ± SD	0.6 ± 0.6	0.6 ± 0.6	0.738
DAS>2.4, n (%)	21 (16)	15 (9)	0.092
DAS≥1.6 - ≤2.4, n (%)	38 (29)	31 (18)	0.056
DAS-remission, n (%)	43 (32)	76 (43)	0.003
Drug-free DAS-remission, n (%)	10 (8)	31 (18)	0.003
ACR/EULAR Boolean remission, n (%)	15 (11)	33 (19)	0.069
SHS progression, year 0-5, median (IQR)/mean ± SD	1 (0-4.5)/2.6±11.2	0.5 (0-3.5)/2.5±4.9	0.116

DAS: disease activity score, ESR: erythrocyte sedimentation rate, VAS: visual analogue scale, HAQ: health assessment questionnaire, RF: rheumatoid factor, ACPA: anti-citrullinated protein antibodies, SD: standard deviation, IQR: interquartile range. ∆ DAS was calculated by extracting the baseline DAS from the current DAS.

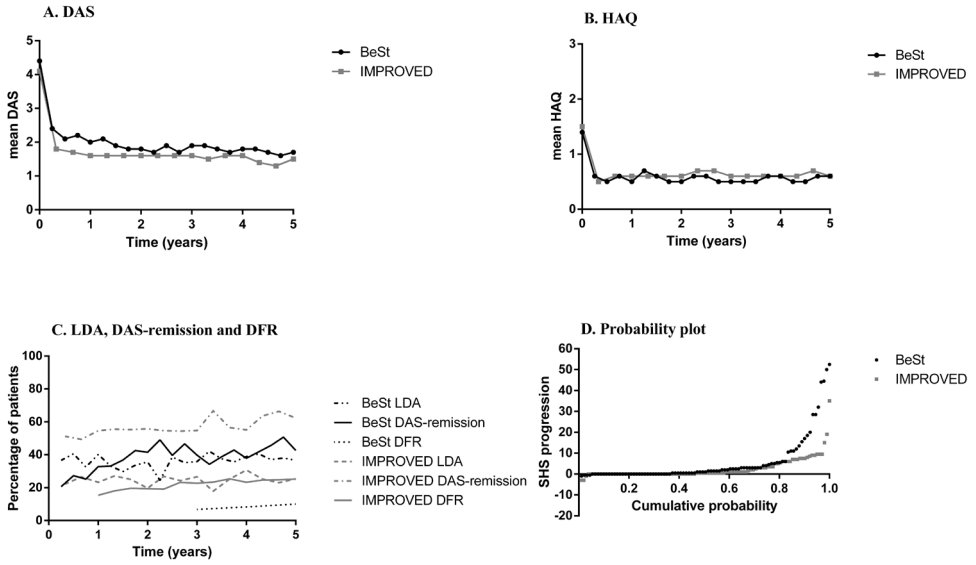


Figure 1: Mean DAS (A), HAQ (B) and percentages in low disease activity, DAS-remission and drug-free DAS-remission (C) during 5 years in the DAS≤2.4 steered (BeSt) patients and the DAS<1.6 steered (IMPROVED) patients and probability plot with radiologic damage progression after 5 year (D).

DAS: disease activity score; HAQ: health assessment questionnaire; LDA: low disease activity DAS≥1.6 - ≤2.4; DAS-remission: DAS<1.6; DFR: drug-free DAS-remission; SHS: Sharp/van der Heijde Score; SHS progression: ≥0.5 points increase after 5 years; 1D: each patient depicted by a dot, ordered along the x-axis from low to high progression scores with individual scores on the y-axis.

At year 1, DAS had decreased similarly in both studies: from baseline by 2.4 in the DAS≤2.4 steered group to 2.0±0.9 and by 2.5 (p=0.445) in the DAS<1.6 steered group to 1.6±1.0 (p=0.004) (table 1 and figure 1A). Functional ability was comparable in both groups (0.5±0.5 (DAS≤2.4) and 0.6±0.6 (DAS<1.6), p=0.148) (table 1 and figure 1B). More patients in the DAS<1.6 steered group than patients in the DAS≤2.4 steered group had achieved DAS<1.6 (51% vs 30%, p<0.001) (table 1 and figure 1C) and Boolean remission (26% vs 16%, p=0.004). Similar percentages in both studies achieved DAS≤2.4 (67% in the DAS≤2.4 steered group and 73% in the DAS<1.6 steered group, p=0.333). By protocol, patients in the DAS≤2.4 steered group could not achieve DFR at year 1. DFR was achieved in 15% of patients in the DAS<1.6 steered group. 93/133 (70%) of patients in the DAS≤2.4 steered group were still on the initial treatment step due to achieving the treatment target. At year 1, SHS progression ≥0.5 was similar in the DAS≤2.4 steered group compared to the DAS<1.6 steered groups (0 (0-1)/0.9±2.3 vs 0 (0-0)/0.4±1.6, p=0.164).

In the univariable regression analysis treatment target (DAS≤2.4 or DAS<1.6) was associated with DAS-remission after 1 year (DAS<1.6 steered group OR 2.47 (95% CI 1.51-4.02)) (table 2). In the multivariable model, corrected for symptom duration, baseline DAS, baseline total

SHS, time on TNF inhibitor and gender, patient group by treatment target was an independent predictor of DAS-remission (DAS<1.6 steered group OR 2.76 (1.52-5.00)).

Table 2: Univariable and multivariable logistic regression analysis with DAS-remission at year 1 as binomial outcome variable

Univariable analysis	**OR**	**95% CI**	**p-value**
DAS<1.6 steered study	2.47	1.51-4.02	<0.001
Age	1.00	0.99-1.02	0.646
Male gender	2.25	1.35-3.76	0.002
Symptom duration	0.99	0.98-1.00	0.013
Baseline DAS	0.63	0.47-0.86	0.003
Tender joint count	0.92	0.88-0.97	<0.001
Swollen joint count	0.97	0.94-1.01	0.138
ESR	0.99	0.99-1.00	0.268
VAS general health	1.00	0.99-1.01	0.894
HAQ	0.93	0.65-1.33	0.687
RF positive	1.20	0.73-1.97	0.470
ACPA positive	0.91	0.57-1.47	0.704
Total SHS	1.03	0.96-1.11	0.460
Time on anti-TNF inhibitor	0.96	0.93-0.98	<0.001
Multivariable analysis			
DAS<1.6 steered study	2.76	1.52-5.00	0.001
Male gender	2.40	1.30-4.42	0.005
Symptom duration	0.99	0.98-1.00	0.075
Baseline DAS	0.74	0.52-1.05	0.090
Total SHS	1.06	0.98-1.15	0.159
Time on anti-TNF inhibitor	0.95	0.93-0.98	0.001

DAS: disease activity score; ESR: erythrocyte sedimentation rate; VAS: visual analogue scale; HAQ: health assessment questionnaire; RF: rheumatoid factor; ACPA: anti-citrullinated protein antibodies; SHS: Sharp/van der Heijde Score; anti-TNF: anti-tumour necrosis factor; OR: odds ratio; CI: confidence interval.

Treatment target was also associated with Boolean remission at year 1 (DAS<1.6 steered group OR 2.31 (1.30-4.14)) (table 3). In the corrected multivariable model for male gender, symptom duration, baseline DAS, RF positive, baseline total SHS and time on anti-TNF inhibitor, treatment target was independently associated with Boolean remission (DAS<1.6 steered group OR 2.60 (1.29-5.25)).

Table 3: Univariable and multivariable logistic regression analysis with ACR/EULAR (Boolean) remission at year 1 as binomial outcome variable.

Univariable analysis	OR	95% CI	p-value
DAS<1.6 steered study	2.31	1.30-4.14	0.005
Age	1.00	0.98-1.02	0.783
Male gender	1.85	1.05-3.26	0.034
Symptom duration	0.99	0.98-1.00	0.195
Baseline DAS	0.79	0.56-1.11	0.171
Tender joint count	0.94	0.89-0.99	0.028
Swollen joint count	1.00	0.96-1.05	0.858
ESR	1.00	0.99-1.01	0.623
VAS general health	1.00	0.99-1.01	0.614
HAQ	1.00	0.66-1.52	0.990
RF positive	1.59	0.86-2.92	0.138
ACPA positive	0.93	0.53-1.62	0.801
Total SHS	0.96	0.86-1.06	0.378
Time on anti-TNF inhibitor	0.95	0.91-0.98	0.004
Multivariable analysis			
DAS<1.6 steered study	2.60	1.29-5.25	0.008
Male gender	1.87	0.97-3.61	0.061
Symptom duration	1.00	0.99-1.01	0.614
Baseline DAS	1.01	0.67-1.52	0.958
RF positive	1.81	0.90-3.63	0.095
Total SHS	1.00	0.89-1.11	0.924
Time on anti-TNF inhibitor	0.94	0.90-0.98	0.006

DAS: disease activity score; ESR: erythrocyte sedimentation rate; VAS: visual analogue scale; HAQ: health assessment questionnaire; RF: rheumatoid factor; ACPA: anti-citrullinated protein antibodies; SHS: Sharp/van der Heijde Score; anti-TNF: anti-tumour necrosis factor; OR: odds ratio; CI: confidence interval.

Long-term response

At year 5, DAS decreased similarly from baseline in both studies: in the DAS≤2.4 steered group by 2.6 points to 1.7±0.8 and by 2.7 (p=0.849) in the DAS<1.6 steered group to 1.5±0.8 (p=0.014). Functional ability was comparable in the DAS≤2.4 steered group (0.6±0.6) and the DAS<1.6 steered group (0.6±0.6, p=0.738). DAS≤2.4 was achieved in 61% in both groups (p=0.092), but DAS<1.6 was achieved in 32% of the DAS≤2.4 steered group compared to 43% of the DAS<1.6 steered group (p=0.003), and DFR in 8% vs 18% (p=0.003). Boolean remission was achieved by 19% in the DAS<1.6 steered group and 11% in the DAS≤2.4 steered group (p=0.069). 60/133 (45%) of the DAS≤2.4 steered group were on the initial treatment step. More patients in the DAS<1.6 steered group used anti-TNF during 5 years compared to the DAS≤2.4 steered group (82/175 (47%) patients vs 29/133 (22%) patients, respectively, p<0.001). Median (IQR) time on anti-TNF was shorter in the DAS<1.6 steered group (16 (8-20) months) compared to the DAS≤2.4 steered group (18 (9-45) months, p=0.011). There was no difference in SHS progression ≥0.5 in both studies (0.5 (0-3.5)/2.5±4.9 vs 1 (0-4.5)/2.6±11.2, p=0.116, respectively). Figure 1D shows the probability plot.

Treatment target was also associated with DFR after 5 years (DAS<1.6 steered group OR 3.13 (95% CI 1.45-6.77)) (table 4). In the multivariable model treatment target was independently associated with DFR (DAS<1.6 steered group OR 4.50 (1.84-11.03)) after correction for symptom duration, baseline DAS, baseline total SHS and time on TNF inhibitor.

Table 4: Univariable and multivariable logistic regression analysis with drug-free DAS-remission at year 5 as binomial outcome variable

Univariable analysis	**OR**	**95% CI**	**p-value**
DAS<1.6 steered study	3.13	1.45-6.77	0.004
Age	1.01	0.98-1.03	0.547
Male gender	1.34	0.66-2.73	0.416
Symptom duration	0.98	0.96-1.00	0.020
Baseline DAS	0.90	0.59-1.37	0.628
Tender joint count	0.94	0.88-1.01	0.091
Swollen joint count	1.01	0.96-1.07	0.758
ESR	1.00	0.99-1.02	0.521
VAS general health	1.01	0.99-1.02	0.530
HAQ	1.34	0.80-2.25	0.270
RF positive	0.50	0.25-1.01	0.053
ACPA positive	0.36	0.18-0.72	0.004
Total SHS	0.90	0.79-1.03	0.128
Time on anti-TNF inhibitor	0.94	0.90-0.99	0.012
Multivariable analysis			
DAS<1.6 steered study	4.50	1.84-11.03	0.001
Symptom duration	0.98	0.97-1.00	0.065
Baseline DAS	0.94	0.58-1.53	0.792
Total SHS	0.94	0.83-1.07	0.350
Time on anti-TNF inhibitor	0.91	0.86-0.97	0.002

DAS: disease activity score; ESR: erythrocyte sedimentation rate; VAS: visual analogue scale; HAQ: health assessment questionnaire; RF: rheumatoid factor; ACPA: anti-citrullinated protein antibodies; SHS: Sharp/van der Heijde Score; anti-TNF: anti-tumour necrosis factor; OR: odds ratio; CI: confidence interval.

DISCUSSION

Treat-to-target therapy is effective in RA patients. It is recommended to set the treatment target at DAS-remission or at least at low disease activity. Previous studies [4;6] showed that patients who achieved remission had better disease outcomes than patients who achieved low disease activity. However, this association may be multifactorial rather than purely causal. A head to head comparison trial might show which is the optimal treatment target. Alternatively, we tried to compare two treat-to-target trials with DAS≤2.4 or DAS<1.6 as treatment target. We found that treatment target indeed appears to be an independent predictor for short term (DAS-remission) as well as long term (DFR) disease outcomes.

Instinctively, we expect treatment-to-target results in more patients achieving the target, regardless of its height. However, a target of remission may be more difficult to achieve than low disease activity and indeed this was seen in this comparison. At the first evaluation of treatment efficacy, similar percentages of patients in both groups had achieved the target (56% of the DAS≤2.4 targeted group and 53% of the DAS<1.6 targeted group). However, as no treatment adjustments have occurred, this seems coincidental and likely to reflect differences in patient and disease characteristics that still remain despite our patient selection. At the end of the first year, despite treatment adjustments, in the DAS≤2.4 steered study the target was achieved in 67% and in the DAS<1.6 steered study in only 51%. After 5 years, these percentages were 61% and 43%, respectively.

Whether or not a treatment target is achieved also depends on the therapies used and on patient and disease characteristics. We tried to maximize similarities between the patient groups as well as therapies by comparing patients from the IMPROVED-study who could have been included in the BeSt-study, with patients from the BeSt-study who received treatment comparable to treatment in the IMPROVED-study. In addition, differences in baseline DAS and SHS, symptom duration, gender and time on TNF-inhibitor were corrected for in the multivariable analysis. In the DAS<1.6 targeted group, baseline DAS (SJC, TJC, but not ESR and VAS global health) were lower than in the DAS≤2.4 targeted group, symptom duration shorter, and baseline radiologic damage less often present. There are also some differences in initial and subsequent therapy: the DAS<1.6 targeted group started with a higher MTX dose, that was only prescribed to the DAS≤2.4 targeted group if after 3 months the DAS remained >2.4, but on the other hand, the DAS<1.6 targeted group did not receive co-treatment with SSZ. We do not expect, but cannot rule out, that these differences in medications have affected the differences in disease outcomes. A recent head to head comparison study [14] has shown that extended combination of prednisolone and MTX with SSZ, is not superior to only prednisolone with MTX. Over time there were also slight differences between both groups: patients who did not achieve the target DAS≤2.4 were treated with a combination of MTX with cyclosporine followed by, if necessary, MTX with infliximab, whereas patients who did not achieve the target DAS<1.6 were randomized to DMARD combination and low dose prednisone, or to MTX with TNF-blocker. After failure on the TNF-blocker, a second biologic DMARD was allowed in the DAS<1.6 steered patient group, but not in the DAS≤2.4 steered patient group. We found that more patients in the DAS<1.6 steered patient group used a TNF blocker.[15;16] Tapering of medication was required in the DAS<1.6 steered patient group more rapidly than in the DAS≤2.4 steered patient group. Probably as a result, median time on a TNF blocker was shorter in the DAS<1.6 steered patient group. We tried to correct for time on TNF-inhibitors in the multivariable regression analysis.

After 1 year, we found that DAS-remission was more often achieved in the DAS<1.6 steered group (51%) than in the DAS≤2.4 steered group (30%). Similar proportions of patients had

achieved DAS≤2.4 (67% in the DAS≤2.4 steered group and 73% in the DAS<1.6 steered group). Decrease in DAS over time compared with baseline was similar in both groups. Also, functional ability over time was not different between the groups. Furthermore, in both groups radiologic progression after 1 and 5 years was similar. After 5 years, DFR was achieved more often in the DAS<1.6 steered group. The multivariable regression analysis shows that the study origin, as proxy for treatment target, was independently associated with DAS-remission, Boolean remission and DFR. It also shows that male patients are more likely to have a favourable disease outcome, as reported before.[6]

There are several limitations to our study. It is clear that despite similarities between the patient groups, they are from 2 studies with differences in recruitment period, inclusion criteria, treatment strategies and therapies and evaluation frequencies, all of which may have influenced our outcomes beyond the effect of steering at different treatment targets. We looked only at patients with high disease activity at baseline, and for patients with low disease activity the outcomes may have been different. Also, 'study group' that was used as proxy for treatment strategy may represent more than the treatment targets. We have insufficient details on use of various medications over time in our patient groups and can only speculate that the DAS<1.6 steered group may have tapered medication more often than the DAS≤2.4 steered group. How this influences our results is unclear. Rapid drug tapering may have resulted in more disease flares, but on the other hand may also have inflated the number of patients in (non-sustained) DFR at various time points. In observational situations, patients who are in (DAS- or clinical) remission have less radiological damage progression than patients in low disease activity. However, this may be a coincidental rather than a causal association. Radiological data after 1 year were based on scores by 2 different teams of independent scorers, although the latter were trained by the former. Also, the scoring method was different in both studies. The BeSt-study was scored in random order and the IMPROVED-study was scored chronologically. We also have not looked at patient reported outcomes or drug side effects that may be more relevant to patients in daily life than DAS and HAQ. Our main focus was to compare the treatment targets in both studies and by comparing the side effects it may not be possible to compare the treatment targets. Also, it is difficult to link side effects with different treatment that patients have received.

Finally, we chose DAS-remission after 1 year as outcome for the regression analysis, the stricter remission definition Boolean remission at year 1 and DAS-remission after discontinuation of all DMARDs as long term outcome, because it most strongly resembles reversal of disease or 'cure'. However, DAS-remission and Boolean remission at 1 year outcome are interrelated with the treatment strategy in at least one of the groups, and through rules of tapering in both protocols, also DFR is interrelated with the treatment targets.

In conclusion, our comparison between 2 treat-to-target cohorts suggests that indeed aiming at a stricter treatment target, DAS-remission, although more difficult to achieve than low disease

activity, results in better disease outcomes in early active RA patients and is associated with DAS<1.6 and Boolean remission at year 1 and DFR at year 5. On the other hand, although the DAS<1.6 steered patients had lower DAS over time, their functional ability (HAQ) over time was similar to that measured in the DAS≤2.4 steered patients. Also, the potentially higher costs of continued DAS<1.6 steered treatment may be a factor that needs to be considered when deciding which is the optimal treatment target for each patient.

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SUPPLEMENTARY FILE

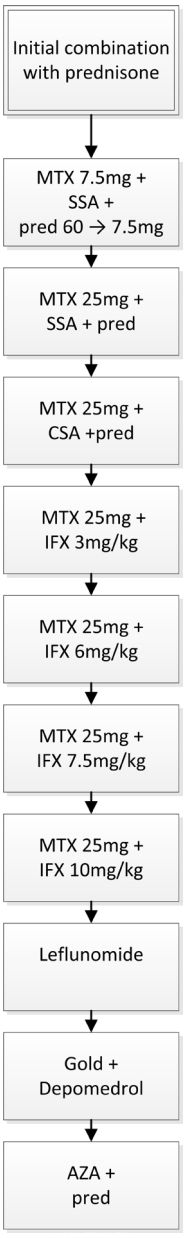

Figure 1: Initial combination with prednisone (arm 3) group BeSt-study flow chart treatment strategy

CSA: ciclosporin A 2.5mg/kg/day; Depomedrol: 3 injections of 120mg in week 1, 4 and 8; Gold 50mg/week; IFX: infliximab, dosages once per 8 weeks; Leflunomide 20mg/day; MTX: methotrexate, dosage per week; Pred: prednisone 7.5mg/day unless indicated otherwise; SSA: sulfasalazine 2000mg/day.

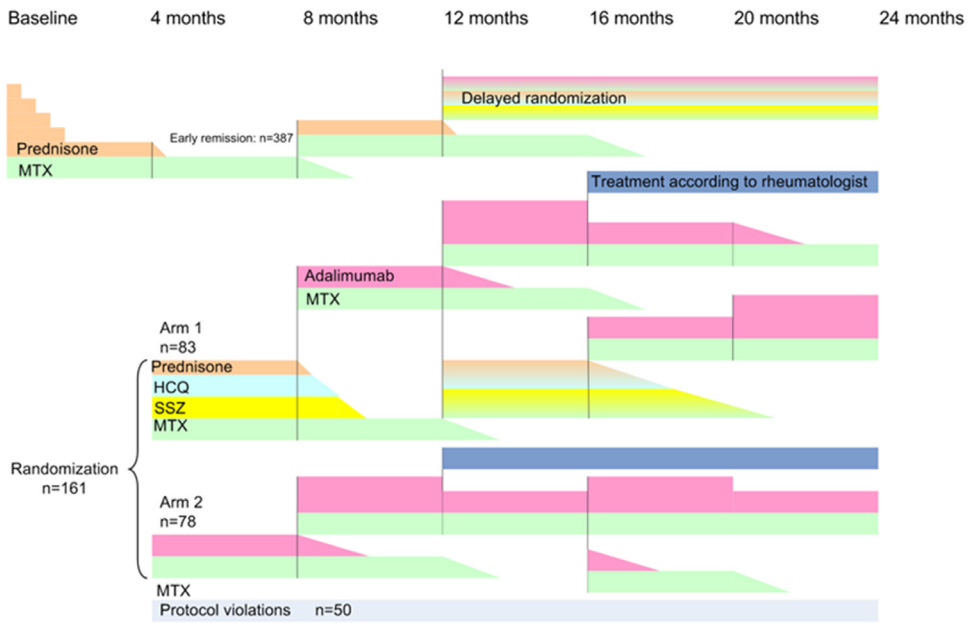

Figure 2: IMPROVED-study flow chart

MTX: methotrexate, 25mg/week; HCQ: hydroxychloroquine; SSZ: sulphasalazine. Colours: orange=prednisone, green=MTX, dark blue=treatment according to opinion rheumatologist (TAR), aqua=HCQ, yellow=SSZ, purple=adalimumab biweekly, double thickness purple=adalimumab weekly, grey=protocol not followed as required but remained in follow-up (outside of protocol, OOP).

All patients started with MTX and prednisone, tapered from 60mg/day to 7.5mg/day in 7 weeks. After 4 months if patients were in DAS-remission (DAS<1.6) prednisone was tapered to MTX monotherapy. If patients were not in DAS-remission they were randomized to arm 1 (MTX 25mg/week, HCQ 400mg/day, SSZ 2000mg/day and prednisone 7.5mg/day) or arm 2 (MTX 25mg/week plus adalimumab 40mg/2 weeks). Every four months if patients were in DAS-remission, the medication was tapered or stopped and if patients were not in DAS-remission, the medication was intensified or restarted.

Chapter 9

RHEUMATOLOGISTS' ADHERENCE TO A DISEASE ACTIVITY SCORE STEERED TREATMENT PROTOCOL IN EARLY ARTHRITIS PATIENTS IS LESS IF THE TARGET IS REMISSION

Gülşah Akdemir, Iris M. Markusse, Yvonne P.M. Goekoop-Ruiterman, Gerda M. Steup-Beekman, Bernard A.M. Grillet, Pit J.S.M. Kerstens, Willem F. Lems, Tom W.J. Huizinga, Cornelia F. Allaart

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ABSTRACT

Introduction/objectives

To compare rheumatologists' adherence to treatment protocols for rheumatoid arthritis (RA) targeted at Disease Activity Score (DAS)≤2.4 or <1.6.

Method

The BeSt-study enrolled 508 early RA (1987) patients targeted at DAS≤2.4. The IMPROVED-study included 479 early RA (2010) and 122 undifferentiated arthritis patients targeted at DAS<1.6. We evaluated rheumatologists' adherence to the protocols and assessed associated opinions and conditions during 5 years.

Results

Protocol adherence was higher in BeSt than in IMPROVED (86% and 70%), with a greater decrease in IMPROVED (from 100% to 48%) than in BeSt (100% to 72%). In BeSt 50% of non-adherence was against treatment intensification/restart, compared to 63% in IMPROVED and 50% vs. 37%, were against tapering/discontinuation. In both studies non-adherence was associated with physicians' disagreement with DAS or with next treatment step and if patient's visual analogue scale (VAS) for general health was ≥20 mm higher than the physician's VAS. In IMPROVED, also discrepancies between swelling, pain, erythrocyte sedimentation rate, and VASgh were associated with non-adherence.

Conclusions

Adherence to DAS steered treatment protocols was high but decreased over 5 years, more in a DAS<1.6 steered protocol. Non-adherence was more likely if physicians disagreed with DAS or next treatment step. In the DAS<1.6 steered protocol, non-adherence was also associated with discrepancies between subjective and (semi)objective disease outcomes, and often against required treatment intensification. These results may indicate that adherence to DAS steered protocols appears to depend in part on the height of the target, and on how physicians perceive the DAS reflects RA activity.

INTRODUCTION

The optimal treatment strategy to suppress disease activity in early arthritis patients is by initial combination therapy followed by targeted treatment.[1-7] Although in clinical trials treat-to-target therapy has been already widely used, implementation in daily practice appears to be difficult.[8-10] Furthermore, it is unknown what the optimum treatment target is. It is recommended to aim at disease activity score (DAS)-remission (<1.6) or low disease activity (DAS<2.4).[11] A lower disease activity seems to be the optimal treatment target with better disease outcomes.[4,7] However, achieving lower DAS and having better disease outcomes may not be causally related, but results of mutually interdependent qualities or characteristics. Remission, especially by the strictest definition, can be difficult to achieve in daily practice. Moreover, steering at remission when disease activity is already low can lead to more costs and side effects with no added clinical benefit. Rheumatologists may be reluctant to aim for remission if disease activity is already substantially decreased from baseline, especially if they feel that the measured DAS is falsely elevated due to symptoms or inflammation not caused by rheumatoid disease activity.

We tried to estimate rheumatologists' willingness and arguments to treat to target if the target was low disease activity or DAS-remission by comparing two clinical trials in patients with RA where the treatment targets were DAS≤2.4 and DAS<1.6. The BeSt-study, a multicentre randomized clinical trial set up in the year 2000, when treat-to-target was not yet part of daily practice. Four different treatment strategies were assessed in early rheumatoid arthritis (RA) patients aiming at low disease activity (DAS≤2.4). Seven years later in rheumatology centers who also participated in the BeSt-study, the IMPROVED-study started, a randomized clinical trial. Early RA and undifferentiated arthritis (UA) patients were treated with methotrexate (MTX) and tapered high dose of prednisone followed by treatment targeted at DAS-remission (DAS<1.6). To investigate whether these treatment targets can be equally well implemented in daily practice, we compared rheumatologists' adherence to these DAS steered treatment protocols targeted at either DAS≤2.4 or DAS<1.6 and assessed associated opinions of the rheumatologists and conditions that may result in non-adherence by the rheumatologist during 5 years follow-up.

MATERIALS AND METHODS

Study design and patients

The BeSt-study (Dutch acronym for treatment strategies) was a multicenter, randomized, clinical trial started in 20 hospitals in the Netherlands in the year 2000, when treat-to-target was not daily practice. The aim was to evaluate the efficacy of 4 treatment strategies in 508 early active

RA according to the 1987 American College of Rheumatology (ACR) criteria.[12] Every 3 months the DAS was measured and calculated by the research nurse and treatment adjustments were initiated by the rheumatologist targeted at low disease activity (DAS≤2.4). If patients did not achieve low disease activity, the next treatment step was taken (supplementary figure 1). If the DAS was ≤2.4 for at least six months, medication was tapered to a maintenance dose. From year 2, if next the DAS was <1.6 for at least six months, medication was discontinued, but when the DAS was ≥1.6 medication was restarted, and subsequently increased or tapered depending on the DAS as mentioned above. The study was approved by the Medical Ethics Committee of each participating center and all patients gave written informed consent. More details about the BeSt-study were previously published.[3,5]

The IMPROVED-study (acronym for Induction therapy with MTX and Prednisone in Rheumatoid Or Very Early arthritic Disease) was a multicenter, randomized, clinical trial started in 2007 in 12 hospitals in the western part of the Netherlands, who also participated in the BeSt-study. 479 early RA according to the 2010 ACR and European League Against Rheumatism (EULAR) classification criteria [13] and 122 UA patients, started with induction therapy with MTX and tapered high dose of prednisone followed by 4-monthly treatment targeted at DAS-remission (<1.6). If patients were in DAS-remission, the medication was tapered and finally stopped but if DAS was >1.6, the medication was intensified or restarted (supplementary figure 2). All patients gave written informed consent and the Medical Ethical Committee of each participating center approved the study protocol. Details about the IMPROVED-study were published elsewhere.[4,7]

Measurements

All treatment steps in both studies were recorded in two different databases. We evaluated whether each treatment step was by protocol or not. Every study visit the rheumatologist was asked to fill out a brief questionnaire about satisfaction with the effect of treatment, agreement with the required treatment step, and agreement with the DAS (table 1). Also, the rheumatologists recorded their estimation of the patient's disease activity on a visual analogue scale (VASphys, 0-100 mm, 0=inactive, 100=most active).

Five hypothetical conditions were formulated that may have an effect in the decision process of the rheumatologist to take a treatment step not by protocol.[14] These conditions aim to represent likely discrepancies between synovitis observed at physical examination and reported pain at physical examination or signs of inflammation in the laboratory analysis and discrepancies between the VASphys and the VAS for global health by the patient (VASgh) as used in calculation of the DAS (table 1).

Table 1: A. brief questionnaire filled out by the physician at every visit, B. five hypothetical conditions.

A.

1. Are you satisfied with the effect of the treatment on the rheumatoid arthritis (undifferentiated arthritis) in this patient?
   - ☐ Yes
   - ☐ No, the disease is not sufficiently suppressed
2. Do you think the DAS adequately represents the disease activity in this patient?
   - ☐ Yes, the situation is well represented by the DAS
   - ☐ No, the patient is doing better than the DAS represents
   - ☐ No, the patient is doing worse than the DAS represents
3. Are you satisfied with the next treatment step?
   - ☐ Yes, I would have taken the same (or comparable) step
   - ☐ No, I would have treated the patient as follows: …

B.

Condition 1	SJC ≤1 and TJC ≥2
Condition 2	SJC ≤1 and ESR ≥28
Condition 3	SJC ≤1 and VASgh ≥20 mm
Condition 4	VASgh ≥20 mm higher than VASphys
Condition 5	VASphys ≥20 mm higher than VASgh

SJC: swollen joint count; TJC: tender joint count; ESR: erythrocyte sedimentation rate; VASgh: visual analogue scale general health of the patient; VASphys: visual analogue scale general health of the patient filled out by the physician.

Statistical analyses

Data of 5 years follow-up from both studies were used. Both studies were compared for frequency of adherence and protocol violations using descriptive statistics. A Generalized Linear Mixed Model (GLMM) for each study was used to evaluate: the association between protocol violations and the answers to the rheumatologists' questionnaire; the association between protocol violations (dependent) and the presence of the hypothetical conditions (independent); the association between the (dis)agreement with the DAS as filled out in the questionnaire by the rheumatologist (dependent) and the presence of the hypothetical conditions (independent); the association between the (dis)agreement with the DAS as filled out on the questionnaire by the rheumatologist (dependent) and DAS categories (independent) (For the BeSt-study 3 DAS categories were used (DAS-remission <1.6, low disease activity ≥1.6 ≤2.4, and high disease activity >2.4) and for the IMPROVED-study 2 categories were used (DAS-remission <1.6, and no DAS-remission ≥1.6)); the association between physician's satisfaction with how effect of treatment (dependent) and DAS categories as mentioned above (independent). An autoregressive moving average was used for the correlation matrix in both studies that assumes that observations that are further apart are less strongly correlated. Statistical analyses were performed with SPSS for Windows version 23.0.

RESULTS

Protocol adherence and violations

Frequencies of protocol adherence and violations per visit during 5 years follow-up are shown in figure 1A for the BeSt-study and in figure 2A for the IMPROVED-study. Of the visit at t=5 years, data were available for 82% of patients in the BeSt-study and in 73% in the IMPROVED-study. Rheumatologists' adherence to the protocol was greater in the BeSt-study than in the IMPROVED-study in completed visits up to the 5th year (mean over time 86% and 70%, respectively). Protocol adherence decreased over time from 100% to 72% in the BeSt-study and from 100% to 48% in the IMPROVED-study. Protocol violations could entail either omitting to restart or intensify medication (as required if DAS was above treatment target: high DAS protocol violation) or omitting to taper or stop (as required if DAS was below treatment target: low DAS protocol violation). Of all protocol violations in the BeSt-study 50% were low-DAS protocol violations and 50% were high-DAS protocol violations. In case of a high-DAS protocol violation the measured DAS was (median) 0.6 (interquartile range IQR 0.3;1.2) higher than the target DAS, whereas the difference was 0.9 (0.4;1.6) when the protocol for high DAS was followed (table 2). In case of a low-DAS protocol violation the measured DAS was 0.7 (-1.2;-0.3) below the target DAS, whereas the difference was -0.9 (-1.4;-0.5) when the protocol for low DAS was followed. Patients' age was associated with more high-DAS protocol violations (1.02 (1.01 – 1.03)), and gender showed a trend (female gender 1.44 (0.94 – 2.21)), but these associations were not found for low-DAS protocol violations. There was no difference in protocol violations between the treatment arms (p=0.872). In both studies, physicians in the peripheral centers had higher adherence compared to those in the two university centers (BeSt-study 95% peripheral vs 87% university and IMPROVED-study 94% vs. 66%, respectively).

Of all protocol violations in the IMPROVED-study, 63% were high-DAS protocol violations and 37% were low-DAS protocol violations. In case of a high-DAS protocol violation, the measured DAS was (median) 0.5 (IQR 0.2;0.9) higher than the target DAS, whereas the difference was 0.7 (0.3;1,2) when the protocol for high DAS was followed. In case of a low-DAS protocol violation, the measured DAS was -0.6 (-0.9;-0.3) lower than the target DAS, whereas the difference was -0.7 (-1.0;-0.4) when the protocol for low DAS was followed. Patient's gender was associated with high-DAS protocol violations (OR for females 1.53 (1.23-1.90)) and age showed a trend (1.01 (1.00-1.02)). Age and gender were not associated with low-DAS protocol violations. Diagnosis of RA (OR 1.47 (1.05-2.06)) and treatment group (arm 1 OR 2.07 (1.36-3.13) and arm 2 OR 1.87 (1.21-2.87)) were associated with more low DAS-protocol violations, and diagnosis RA was associated with *fewer* high-DAS protocol violations (OR 0.73 (0.56-0.95)). Both arm 1 (OR 1.44 (1.13-1.85)) and arm 2 (1.69 (1.31-2.19)) were also associated with more high-DAS protocol violations in the IMPROVED-study. As expected, there were

more protocol violations in the Outside of Protocol group (OR for high-DAS protocol violations 2.84 (2.05-3.94)).

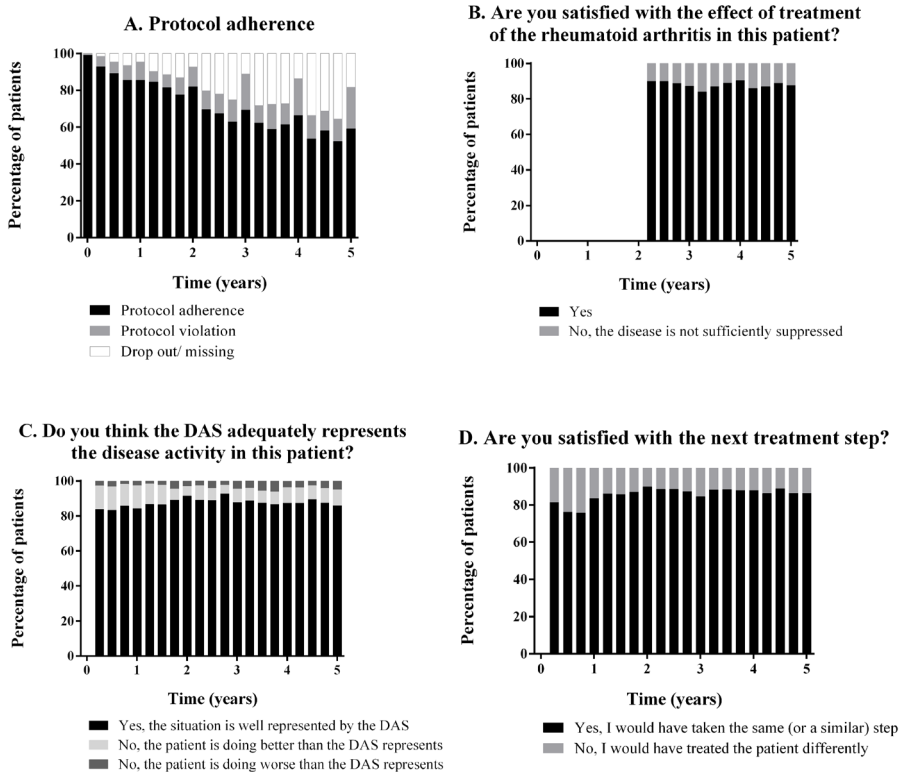

Figure 1: Protocol adherence and violations in the BeSt-study and answers of the rheumatologist to the questionnaire

Note: A: protocol adherence was evaluated every visit; B: question was asked every visit from the 10th visit in year 3 until the end of follow-up; C: question was asked every visit from the 2nd visit until the end of follow-up; D: question was asked every visit from the 2nd visit until the end of follow-up.

DAS: disease activity score

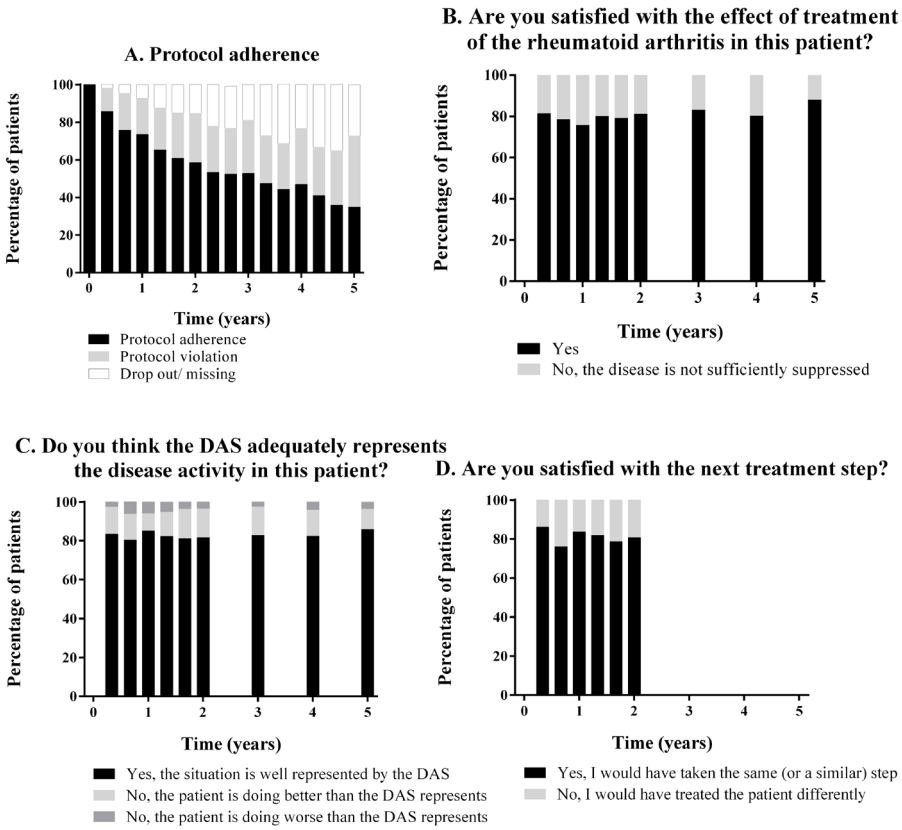

Figure 2: Protocol adherence and violations in the IMPROVED-study and answers of the rheumatologist to the questionnaire
Note: A: protocol adherence was evaluated every visit; B: question was asked every visit from the 2nd visit and after the 2nd year only at yearly visits; C: question was asked every visit from the 2nd visit and after the 2nd year only at yearly visits; D: question was asked every visit from the 2nd visit until the 7th visit.
DAS: disease activity score

In the BeSt-study rheumatologist were more likely not to follow the protocol if they were not satisfied with the current treatment effect (OR (95% CI) 1.36 (1.08-1.71)), disagreed with how the DAS represented actual disease activity (2.26 (1.84-2.78) when they thought the DAS overestimated disease activity and 2.82 (2.08-3.81) when they thought the DAS underestimated disease activity), were not satisfied with the current treatment effect (OR (95% CI) 1.36 (1.08-1.71)) or disagreed with the next treatment step (2.77 (2.34-3.28)) (table 3). However, in 346/463 (75%) visits where the rheumatologist was not satisfied with the current treatment effect the protocol was still followed, as also occurred in 714/939 (76%) visits where the rheumatologist disagreed with how the DAS represented actual disease activity, and in 832/1070 (78%) visits where the rheumatologist did not agree with the next treatment step.

Table 2: Differences with DAS-target in protocol violations (high-DAS or low-DAS) and no protocol violations.

	BeSt-study Target 2.4				IMPROVED-study Target 1.6			
	High DAS		Low DAS		High DAS		Low DAS	
	PV	No PV	PV	No PV	PV	No PV	PV	No PV
mDAS, mean±SD	3.2±0.7	3.5±0.9	1.6±0.6	1.5±0.6	2.2±0.5	2.4±0.6	1.0±0.4	0.9±0.4
Delta mDAS tDAS,	0.8±0.7	1.1±0.9	-0.8±0.6	-0.9±0.6	0.6±0.5	0.8±0.6	-0.6±0.4	-0.7±0.4
mean±SD	0.6	0.9	-0.7	-0.9	0.5	0.7	-0.6	-0.7
median (IQR)	(0.3;1.2)	(0.4;1.6)	(-1.2;-0.3)	(-1.4;-0.5)	(0.2;0.9)	(0.3;1.2)	(-0.9;-0.3)	(-1.0;-0.4)

DAS: disease activity score; PV: protocol violation; mDAS: measured DAS; tDAS target DAS.

Table 3: GLMM outcomes with protocol violation as dependent variable and opinions and conditions as independent variables.

	BeSt			IMPROVED		
Opinions	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Not satisfied with treatment effect	1.36	1.08-1.71	0.010	0.59	0.49-0.72	<0.001
Disagreement with DAS (felt overestimation of actual disease activity)	2.26	1.84-2.78	<0.001	5.97	4.82-7.40	<0.001
Disagreement with DAS (felt underestimation of actual disease activity)	2.82	2.08-3.81	<0.001	1.44	1.01-2.07	0.047
Not satisfied next treatment step	2.77	2.34-3.28	<0.001	3.53	2.84-4.37	<0.001
Conditions						
1	1.00	0.85-1.18	0.993	3.1	2.73-3.52	<0.001
2	1.03	0.80-1.33	0.826	1.74	1.42-2.14	<0.001
3	1.04	0.89-1.22	0.629	2.03	1.80-2.29	<0.001
4	1.34	1.14-1.57	<0.001	2.18	1.85-2.56	<0.001
5	1.36	1.00-1.86	0.050	0.89	0.64-1.24	0.493

DAS: disease activity score; OR: odds ratio; CI: confidence interval.

Compared to the BeSt-study, in the IMPROVED-study a protocol violation appeared even more likely if rheumatologists disagreed with how the DAS represented actual disease activity (5.97 (4.82-7.40) if they thought the DAS overestimated disease activity and 1.44 (1.01-2.07) if they thought the DAS underestimated disease activity) or disagreed with the next treatment step (3.53 (2.84-4.37)). However, if they were not satisfied with the current treatment effect this was associated with fewer protocol violations (0.59 (0.49-0.72)). In 299/647 (46%) visits there was still protocol adherence although the rheumatologist disagreed with the DAS, as in 280/475 (59%) visits where the rheumatologist was not satisfied about the next treatment step and 565/736 (77%) visits where the rheumatologists were not satisfied with the effect of current treatment.
When testing the five hypothetical conditions, in the BeSt-study more protocol violations were likely if the VASgh was ≥20 mm higher than the VASphys (1.34 (1.14-1.57)) (condition 4, table 1). In the IMPROVED-study this association was also found (2.18 (1.85-2.56)). In addition, the risk of a protocol violation was also higher if the swollen joint count (SJC) was ≤1 but tender joint count (TJC) was ≥2 (3.1 (2.73-3.52)) (condition 1, table 1) or SJC was ≤1 and the erythrocyte sedimentation rate (ESR) was ≥28 (1.74 (1.42-2.14)) (condition 2, table 1), and or SJC was ≤1 and VAS patient was ≥20 (2.03 (1.80-2.29)) (condition 3, table 1). In the BeSt-study these associations were not found.

Agreement with how the DAS represents actual disease activity in relation to treatment targets

The rheumatologist answered that the actual disease activity was well represented by the DAS in 87% of visits in the BeSt-study and 83% in the IMPROVED-study (figures 1C and 2C). If misrepresentation of actual disease activity was suspected, the rheumatologists mostly felt that the patient was doing better than the DAS indicated and only rarely did they report to feel that the measured DAS underestimated actual disease activity. In the BeSt-study, the higher the DAS, the more likely that rheumatologists suspected overestimation of disease activity (by category: DAS>2.4: 97.29 (58.45-161.93), DAS≥1.6 but ≤2.4: 9.86 (5.88-16.53)) (table 4). Also as a continuous variable a higher DAS was associated with more reports of DAS overestimating actual disease activity (2.97 (2.72-3.24)). In the IMPROVED-study a DAS ≥1.6 was more often associated with reports of overestimated actual disease activity (22.03 (16.65-29.15), for DAS as continuous variable 3.68 (3.25-4.16)).
Both in the BeSt-study and the IMPROVED-study, rheumatologists were more likely to report that the DAS overestimated actual disease activity if VASgh was ≥20mm higher than the VASphys (condition 4) (table 4). If SJC≤1 and VASgh ≥20mm (condition 3) (0.76 (0.64-0.91)) in the BeSt-study DAS overestimation was less often reported, in contrast to the IMPROVED-study where this condition was associated with more DAS overestimation (3.03 (2.51-3.66)). In the IMPROVED-study the rheumatologists answered that there was a DAS overestimation

if SJC ≤1 and TJC ≥2 (condition 1) (5.65 (4.67-6.84)) and SJC ≤1 and ESR ≥28 (condition 2) (1.88 (1.39-2.55)).

DAS underestimation was filled out by the rheumatologists if the DAS was higher in the BeSt-study (category ≥1.6-≤2.4 (1.40 (1.11-1.77)), category DAS<1.6 (0.53 (0.40-0.70))) (table 4). In the IMPROVED-study if the DAS was <1.6 the rheumatologists did not feel that the DAS was underestimating the disease activity (0.48 (0.38-0.60)). Increase in DAS was associated with more DAS underestimation in both studies (BeSt-study: 1.39 (1.25-1.55) and IMPROVED-study 1.95 (1.70-2.25)). Condition 5 (VASphys ≥20mm higher than VASgh) was in both studies associated with DAS underestimation (6.73 (5.00-9.06) BeSt-study and 8.21 (5.80-11.61) IMPROVED-study).

Table 4: GLMM outcomes with DAS over/underestimation as dependent variable and DAS and conditions as independent variables.

	BeSt			IMPROVED		
Dependent: DAS overestimation	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
DAS <1.6	ref			ref		
DAS ≥1.6-≤2.4	9.86	5.88-16.53	<0.001	22.03	16.65-29.15	<0.001
DAS >2.4	97.29	58.45-161.93	<0.001			
DAS	2.97	2.72-3.24	<0.001	3.68	3.25-4.16	<0.001
Conditions						
1	0.87	0.73-1.03	0.096	5.65	4.67-6.84	<0.001
2	1.16	0.88-1.52	0.300	1.88	1.39-2.55	<0.001
3	0.76	0.64-0.91	0.002	3.03	2.51-3.66	<0.001
4	2.96	2.51-3.49	<0.001	4.49	3.68-5.48	<0.001
Dependent: DAS underestimation						
DAS<1.6	0.53	0.40-0.70	<0.001	0.48	0.38-0.60	<0.001
DAS ≥1.6-≤2.4	1.40	1.11-1.77	0.005	ref		
DAS >2.4	ref					
DAS	1.39	1.25-1.55	<0.001	1.95	1.70-2.25	<0.001
Condition						
5	6.73	5.00-9.06	<0.001	8.21	5.80-11.61	<0.001
Dependent: satisfied with treatment effect						
DAS<1.6	76.48	53.67-108.98	<0.001	26.06	20.68-32.84	<0.001
DAS ≥1.6-≤2.4	10.07	7.95-12.76	<0.001	ref		
DAS >2.4	ref					
DAS	0.09	0.08-0.11	<0.001	0.07	0.06-0.08	<0.001

DAS: disease activity score; OR: odds ratio; CI: confidence interval.

Satisfaction with the current treatment in relation to treatment target

Satisfaction with the effect of the current treatment was in 88% of the visits in the BeSt-study (figure 1B) and 81% in the IMPROVED-study (figure 2B). In the BeSt-study, if the DAS was low rheumatologists were more often satisfied with the current treatment effect (<1.6: 76.48 (53.67-108.98) and ≥1.6-2.4: 10.07 (7.95-12.76)) (table 4). In the IMPROVED-study, DAS<1.6 resulted in more satisfaction with the treatment effect (26.06 (20.68-32.84)). If the DAS increased rheumatologists became less satisfied with the current treatment effect in both studies (BeSt-study: 0.09 (0.08-0.11) and IMPROVED-study 0.07 (0.06-0.08)).

Satisfaction with the next treatment step was 76-84% during the first year of the BeSt-study (figure 1D). During 5 years the satisfaction of rheumatologists with the next treatment step increased to 86%. In the IMPROVED-study this question was not asked to the rheumatologists after the 2nd year. During the first year 76-86% of the rheumatologists were satisfied with the treatment step and in the second year this percentage slightly decreased to 80% (figure 2D).

DISCUSSION

Treatment to target is recommended for treatment of patients with RA, but in daily practice it may be challenged by rheumatologists' willingness to conform to protocolled treatment adjustments aiming at a predefined target. Non-adherence may diminish the effect of a treat to target protocol, but both the protocol and the target may diminish adherence. In this study we investigated the target-effect. We compared adherence to two treatment protocols, one aimed at achieving low disease activity (DAS≤2.4, in the BeSt-study) and one aiming at achieving DAS-remission (DAS<1.6, in the IMPROVED-study), and found that protocol adherence was higher in the DAS≤2.4 targeted study. Protocol adherence decreased over time in both studies, but more in the DAS<1.6 targeted study. This was not particularly due to antagonism towards the required tapering of treatment as soon as DAS<1.6 was achieved at a four-monthly evaluation time point, as we found that protocol violations occurred more often against treatment intensification than against tapering. In the DAS≤2.4 steered study, which had more delayed tapering strategies, this was equal. In both studies violations were associated with rheumatologists' disagreement with how the measured DAS represented actual disease activity, or with the next treatment step, and with a patient's VASgh that was ≥20 mm higher than the physicians VAS-disease activity. In the DAS<1.6 steered study apparent discrepancies between number of swollen and painful joints, measured ESR and reported VASgh were associated with more violations compared to the DAS≤2.4 steered study.

Following a protocol that aims at a stricter treatment target is more difficult. It may be felt that there is no additional clinical benefit to be achieved, or there are perceived risks, for instance of side effects and/or higher costs, which may reduce physician's compliance. In

addition, there may be doubt whether the composite score used to measure disease activity does represent actual disease activity.[15] This is certainly suggested by our finding that rheumatologists reported more often that they felt the measured DAS overestimated actual disease activity in a DAS<1.6 steered treatment protocol compared to a DAS≤2.4 steered treatment protocol. When in the DAS<1.6 steered study the DAS approaches the target, rheumatologists also appear more sensitive to apparent discrepancies between subjective and (semi)objective representations of disease activity and reluctant to steer by DAS alone. Still, median differences between measured DAS and target DAS, relative to whether or not the rheumatologist adhered to the protocol, may represent a tendency of the rheumatologists to try to stay closer to the target DAS<1.6 than they did to the target DAS≤2.4. This suggests a learning effect, where between the start of the BeSt-study in 2000 and the start of the IMPROVED study in 2007, rheumatologists have conformed and became accustomed to DAS targeted treatment and agree with the idea that DAS-remission is a target worth aiming for. In addition, they also seem to agree that relatively rapid and complete drug tapering in patients with early RA or undifferentiated RA, should be tried as soon as DAS<1.6 is achieved, as protocol violations were less often against low DAS than against high DAS.

We are the first to compare treatment targets in DAS steered treatment protocols in early arthritis patients by comparing protocol adherence and protocol violations in a long follow up period of 5 years, having access to two such studies with similar technical protocols but aiming at different DAS targets, conducted by largely the same rheumatologist. Both studies were embedded in daily practice in rheumatologists' office, and our results may reflect their willingness to conform to targeted treatment protocols outside clinical trials. There were a lot of differences between the 2 studies that make it difficult to compare them head to head. The IMPROVED-study also included UA patients next to RA patients whereas in the BeSt study all patients had RA. In the BeSt-study patients had a more severe disease and the target was not strict compared to the IMPROVED-study. Furthermore, RA was associated with more low DAS-protocol violations. This may indicate that RA is considered as a more severe disease than UA.

Our results suggest that a DAS steered treatment can be implemented in daily practice. If there is a defined target, the chance to achieve the target is eventually high. However, a stricter treatment target is more difficult to implement in daily practice, because rheumatologists will be content with a slightly higher DAS if they feel it does not represent actual disease activity. Perceived risks of the required steps may reduce physicians' adherence. This however can negatively influence patient outcomes.

The COBRA study aimed at DAS-remission, and showed comparable protocol violations during 6 months follow up (24%).[16] Recently a sub analysis of the NEO-RACo study showed that physicians' better adherence to a protocol steered at modified ACR remission [17] was associated with better clinical outcomes and a lower rate of prescription of biologic DMARD

in later years.[18] Also in other diseases, physicians' adherence to a treatment protocol was associated with better outcomes.[19-22] It is clear that a stricter DAS target may not be achievable in all patients. Patient factors, type of disease, comorbidities, and drug-related risks may affect components of the DAS or prevent further treatment adjustments. Ideally, the optimal treatment target is clear for each patient, allowing individualized treatment.[23]

In conclusion, adherence to two DAS steered treatment protocols was high, but adherence decreased over 5 years. This decrease was more distinct in a DAS<1.6 steered protocol, where violations were more likely if the physician disagreed with the measured DAS. Protocol violations were then more often against required treatment intensification than against required tapering, whereas with a target DAS≤2.4 this was balanced. Also, in a DAS<1.6 steered protocol violations occurred more often in case of potential discrepancies between detected joint swelling, pain and ESR. Our results may indicate that adherence to DAS steered protocols appears to depend at least in part on the height of the target, and in addition on how physicians perceive the DAS reflects RA activity. Targeted treatment is important to achieve the best possible outcomes for RA patients. It would be preferable to combine the trend to set ever stricter treatment targets with the benefits of an individualized approach.

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SUPPLEMENTARY FILE

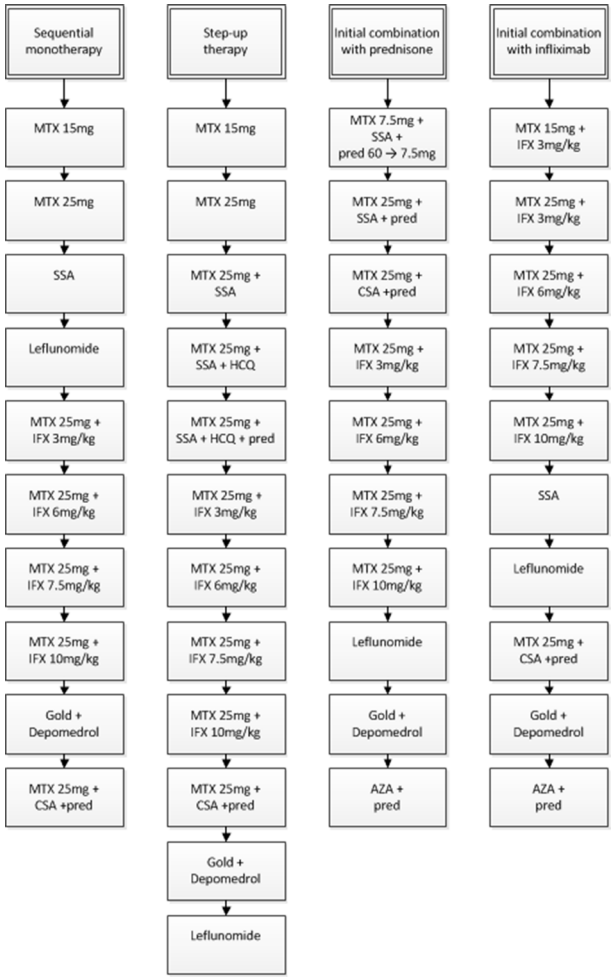


Figure 1: BeSt-study flow chart treatment strategies
AZA: azathioprine 2-3mg/kg/day; CSA: ciclosporin A 2.5mg/kg/day; Depomedrol: 3 injections of 120mg in week 1, 4 and 8; Gold 50mg/week; HCQ: hydroxychloroquine 200mg/day; IFX: infliximab, dosages once per 8 weeks; leflunomide 20mg/day; MTX: methotrexate, dosage per week; Pred: prednisone 7.5mg/day unless indicated otherwise; SSA: sulphasalazine 2000mg/day.

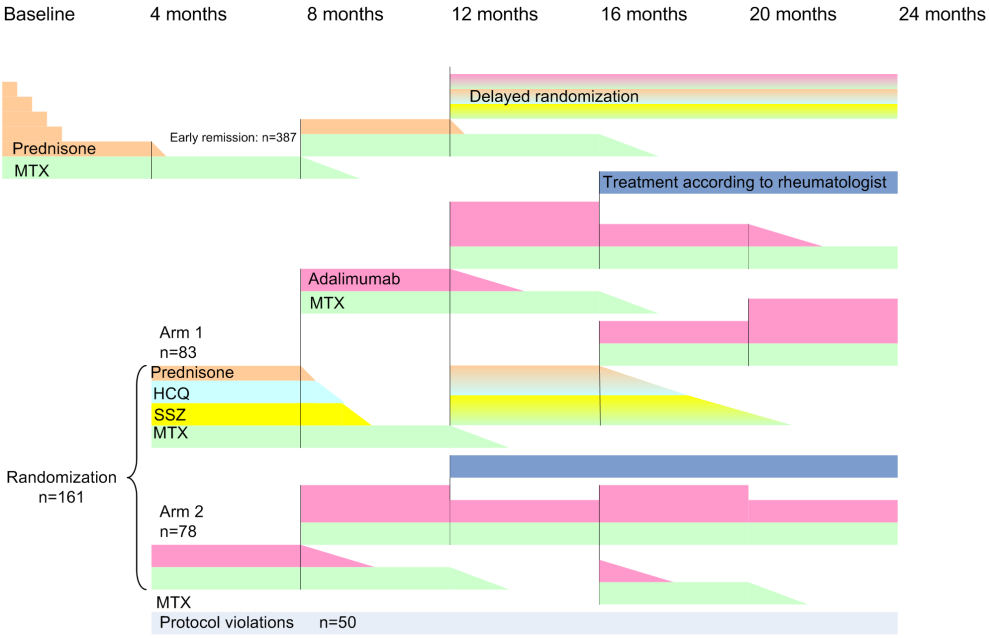


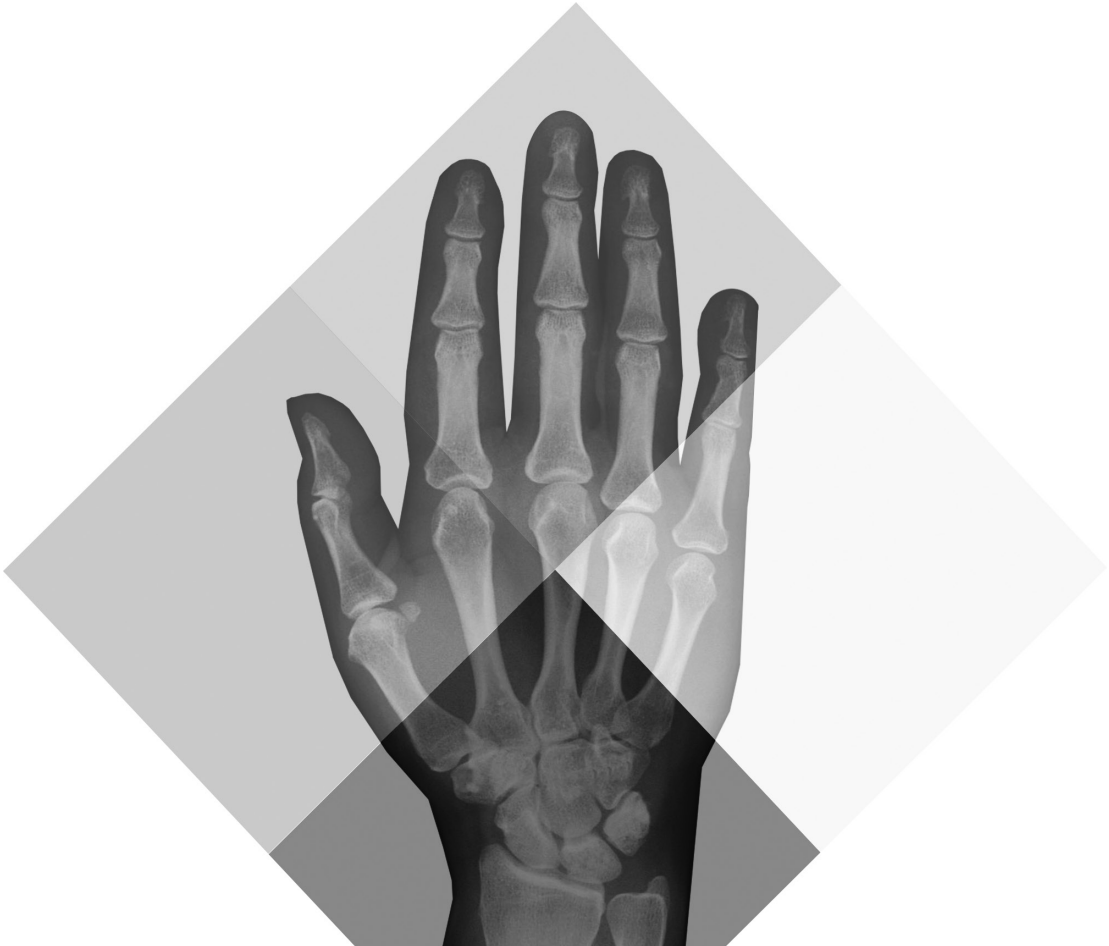
Figure 2: IMPROVED-study flow chart

MTX: methotrexate, 25mg/week; HCQ: hydroxychloroquine; SSZ: sulphasalazine. Colours: orange=prednisone, green=MTX, dark blue=treatment according to opinion rheumatologist (TAR), aqua=HCQ, yellow=SSZ, purple=adalimumab biweekly, double thickness purple=adalimumab weekly, grey=protocol not followed as required but remained in follow-up (outside of protocol, OOP).

All patients started with MTX and prednisone, tapered from 60mg/day to 7.5mg/day in 7 weeks. After 4 months if patients were in remission (DAS<1.6) prednisone was tapered to MTX monotherapy. If patients were not in remission they were randomized to arm 1 (MTX 25mg/week, HCQ 400mg/day, SSZ 2000mg/day and prednisone 7.5mg/day) or arm 2 (MTX 25mg/week plus adalimumab 40mg/2 weeks). Every four months if patients were in remission, the medication was tapered or stopped and if patients were not in remission, the medication was intensified or restarted.

Chapter 10

SUMMARY AND CONCLUSION



At the basis of this thesis is our aim to improve the outcomes of patients with rheumatoid arthritis or undifferentiated arthritis (UA). Research in the past decades has shown that RA patients should be treated as soon as possible and that the optimal treatment to gain rapid improvement is by combination therapy including corticosteroids, or a biologic DMARD, followed, in case of insufficient response, by a treat-to-target regimen. Targeted treatment aimed at DAS-remission (DAS<1.6) or at least low disease activity (DAS≤2.4) has been recommended to avoid clinical deterioration and irreversible damage due to inflammation. If remission is achieved, medication may be tapered, and if remission is achieved early, within a so-called 'window of opportunity', it may be possible that chronicity of inflammation is altogether prevented and prolonged drug-free remission achieved. To investigate this, the IMPROVED study was designed, and data on the 5- year outcomes, and possible objections to further implementation of results, were discussed in chapter 4. of this thesis. Other chapters focussed on potential further improvements for patients with specific rheumatologic conditions, such as autoantibody negative RA, where there is a lower risk for joint damage progression and an uncertainty as to the best treatment strategy, and chronic arthritis of a knee, where local treatment is prefered, but the optimal medication uncertain. Here we briefly look back to the results of our studies, and then towards the future.

THE IMPROVED STUDY

The IMPROVED study the first treatment strategy study to include early (≤2 years) RA based on the revised classification criteria (capturing earlier disease) and unclassified, but clinically suspected of RA, UA patients, and to treat all patients aiming to achieve early drug-free DAS-remission (DFR). All patients started with intensive induction therapy (methotrexate (MTX) and a tapered high dose of prednisone) in the first 4 months followed by DAS-remission (DAS<1.6) steered treatment every 4 months, followed up for 5 years. This targeted treatment therapy resulted in the achievement of DAS-remission in 61% of patients after 4 months of induction therapy.[1] Patients who achieved DAS-remission after 4 months of treatment started tapering medication, until drug-free DAS-remission could be achieved from 1 year after treatment start. Loss of DAS-remission required restart of last effective treatment. Patients who did not achieve DAS-remission after 4 months were randomized to triple therapy (MTX, hydroxychloroquine and sulfasalazine) with prednisone (arm 1) or MTX plus adalimumab (arm 2). Functional ability improved in all patients after 4 months of induction therapy and aproached normal values in the early DAS-remission group and slightly worse values in the other groups. After 1 year, DAS-remission was achieved by 54% of patients and 21% of patients were in DFR.[2] After 2 years 49% of patients were in DAS-remission and 21% in DFR (**chapter 2**). After 5 years, these percentages were similar: 48% were in DAS-remission and

22% in DFR (**chapter 4**). UA patients already had a milder disease at baseline compared to the RA patients and less autoantibody positivity. Still, percentages in DAS-remission were comparable during 5 years in RA and UA patients, but more UA patients did achieve DFR than RA patients, at year 1 (30% vs 19%),[2] at year 2 (34% vs 19%, **chapter 2**) and at year 5 (33% vs 19%, **chapter 4**). Also, autoantibody (rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA)) negative patients more often achieved DFR, indicating milder disease. This suggests that UA patients were in an earlier, not yet chronic phase of the disease or that they and autoantibody negative patients had self-limiting disease.
Patients who achieved early DAS-remission at 4 months had better functional ability and more often achieved DAS-remission and DFR than patients that did not achieve early DAS-remission at 4 months and who were thus randomized. Patients in early DAS-remission already had milder disease at baseline. The change in DAS and HAQ was similar in all patients. This suggests that patients who start with a milder disease achieved better outcomes due to the lower starting values, not due to a stronger improvement. The majority of patients (75%) who were randomized to arm 1 switched to treatment as in arm 2 after failing on DMARD combination therapy or failing after restart of this initial combination therapy. There were also 50 patients who were not in DAS-remission at 4 months and who were not randomized according to the protocol, because there was discrepancy between the DAS measured by the research nurse and the DAS measured by the rheumatologist. These patients were treated according to their rheumatologist following a treat-to-target approach and showed similar results as the randomized patients.

JOINT DAMAGE

Induction therapy followed by DAS-remission steered treatment results in minimal joint damage in most RA and UA patients after 2 years (**chapter 2**). Only 8% (50/610) of patients showed radiological progression. Also, after 5 years joint damage was well suppressed (**chapter 4**). UA patients and autoantibody negative patients had the least joint damage progression. In comparison with other studies[3-5] patients in the IMPROVED study showed less radiological damage progression. In this group of patients where disease activity was generally low and joint damage was minimal, it can be informative to look at what factors are associated with and potentially driving radiologic progression in these patients unconnected to (suppression of) inflammation. We looked at factors that can predict radiological progression after 2 years and found that age and autoantibody positivity (combination of ACPA and anti-carbamylated protein antibodies (anti-CarP)) were associated with radiologic progression (**chapter 3**). Joint damage was mainly caused by progression in joint space narrowing rather than progression of erosions in these patients. A possible explanation could be that increasing age may result

in primary hand osteoarthritis causing joint space narrowing in these patients.[6] Autoantibody positivity is associated with severe disease and more joint damage.[7] Autoantibody positivity may represent a phenotype with particularly bad prognosis. Finding predictive factors in RA and UA patients with minimal damage progression will only be relevant for understanding RA phenotypes, since minimal damage progression will not be relevant in clinical practice.

In another study (the BeSt study) we focussed on joint space narrowing scores and progression in different age groups (**Chapter 7**). The BeSt-study is a multicenter, randomized clinical trial in recent-onset active RA patients randomized to 4 treatment strategies aiming at low disease activity (DAS≤2.4) at 3 monthly intervals.[3] We hypothesized that progression in joint space narrowing and predictors of joint space narrowing may be different between different age groups, due to primary osteoarthritis becoming more prominent with increasing age. Age specific risk factors for the development of joint space narrowing were compared in 3 age groups (≤40, >40 & ≤55 and ≥55). Older RA patients (≥55 years) showed more often and more severe joint space narrowing at baseline than younger patients. Older patients had higher ESR and higher erosion scores indicating rheumatoid inflammation compared to younger patient who had higher swollen joint count. After 10 years of follow up there was no difference in joint space narrowing between the age groups, however patients ≤40 years had higher joint space narrowing progression scores. Risk factors for joint space narrowing were slightly different between the age groups. In patients ≥55 years, autoantibodies and a high ESR were independently associated with joint space narrowing progression after 10 years. In the >40 ≤55 years age group there were no independent predictors of joint space narrowing progression. In the <40 years age group, components of the DAS indicating inflammation (swollen joint count and ESR over time) were indepently associated. In the older age groups primary osteoarthritis may have resulted in joint space narrowing. This may have an effect on how radiologic scoring methods can be interpreted to represent treatment effects of antirheumatoid therapy in different age groups.

INTRA-ARTICULAR INJECTIONS

Isolated monoarthritis can be treated with an intra-articular injection with corticosteroids, however there is a high recurrence rate and reinjection cannot be given endlessly in the same joint.[8] Alternatively, intra-articular injection with a TNF inhibitor can be tried, but studies have shown that this does not appear to be clinically superior to intra-articular injections with corticosteroids.[9-13] To investigate a possible explanation for this, the RIA (Remicade Intra Articularly) study,[13] a double blind randomized controlled trial in patients with chronic gonarthritis with different underlying diseases that persisted or recurred after previous intra-articular corticosteroid treatment, included pre- and post-injection magnetic resonance (MR)

imaging. MR signs correlate well with histological findings [14] and these signs may improve early after intra-articular corticosteroid injection.[15] Patients were randomized to intra-articular treatment with infliximab (a tumour necrosis factor α blocker) or to intra-articular methylprednisolone and clinical outcomes after 6 months were compared. The clinical results showed that infliximab was not superior over prednisolone. All patients who received infliximab had persistent or relapsed gonarthritis after 6 months, whereas 6 of 13 initial injections with methylprednisolone were still effective after 6 months. [13] We hypothesized that either the pre-treatment amount of inflammation was too high to (permanently) improve after local injection, or that initial improvement may have occurred but untreated disease mechanisms have resulted in recurrence of inflammation. In **chapter 5** we focussed on pre-injection MR scores and changes in MR scores after treatment with either intra-articular infliximab or methylprednisolone injections in relation to clinical response in patients with chronic or recurrent gonarthritis with different diagnoses. We found that similar signs of inflammation were seen in intra-articular treatment with infliximab and methylprednisolone. There was a reduction of inflammation and effusion after 4 weeks in knees treated with intra-articular infliximab and methylprednisolon. In infliximab injected knees this was a significant reduction in contrast to methylprednisolone injected knees. This change was associated with early clinical response, measured with a Clinical Knee Joint Score (knee tenderness (0-3), knee swelling (0-3) and patient's VAS for knee pain (0-1)). However, after 6 months there was no association between MR scores or changes in scores. All infliximab injected knees showed recurrence and this was 50% in methylprednisolone injected knees. A recurrence was not associated with MR changes, however methylprednisolone injected knees which showed early clinical improvement may be less likely to relapse after 6 months. Which may be related with the mode of action of the two different medications.

ACPA-NEGATIVE RA

Research focuses mainly on the presence of ACPA, because this results in a severe disease in RA patients with more joint damage and less achievement of DFR.[16-21] The reverse of this was also seen in **chapter 2 and 4,** where ACPA-negative RA and UA patients had less joint damage progression and achieved more DFR than ACPA negative patients. ACPA-negative RA might be a different disease entity compared to ACPA-positive RA[22-24] and therefore might be treated in a different way.[25] However, what this treatment should be has to be clarified. It is suggested that ACPA-negative RA would not need intensive treatment, because ACPA-negative RA patients are less likely to develop joint damage and more likely to achieve DFR. In a subanalysis of the BeSt-study (**chapter 6**) we investigated which initial treatment strategy is more effective in ACPA-negative RA patients. A previous analysis of the BeSt-study showed

that there were no differences in clinical response between ACPA-negative and ACPA-positive patients.[21] Initial combination therapy was more effective in ACPA-negative RA patients, resulting in earlier functional improvement than initial monotherapy, without additional adverse events. The initial combination therapy was effective in a substantial number of ACPA-negative patients. They could taper to monotherapy after 1 year. Patients who failed on MTX monotherapy also responded less to the second step with sulfasalazine. During 10 years of targeted therapy there was no difference between outcomes between combination therapy and monotherapy treatment and damage progression was low in both treatment groups. In early active RA patients initial treatment should focus on rapid relief of symptoms and there is no reason to weigh the initial treatment choice based on the ACPA status.

TREATMENT TARGET

Initial combination therapy followed by a treat-to-target strategy is the optimal treatment strategy to suppress disease activity in early arthritis patients.[1-3,26-28] The optimum treatment target is under discussion. Recommendations state that treatment should be steered at achieving remission (DAS<1.6) or at least at low disease activity (DAS≤2.4).[29] We had two clinical trials performed in the same hospitals in early RA patients that were treated with a treat-to-target strategy aiming at two different treatment targets. The BeSt study was set up in 2000 introducing targeted treatment aiming at low disease activity (DAS≤2.4) at 3 monthly intervals. The IMPROVED study started 7 years later aiming at DAS-remission (DAS<1.6) at 4 monthly intervals. In **chapter 8** we compared these two trials to assess which treatment target is more effective in early RA patients. To compare the patients of 2 different studies we selected patients that were comparable: early active RA patients according to the 1987 criteria[30] from the IMPROVED study that would have fulfilled the inclusion criteria of the BeSt study (≤2 years symptom duration, ≥6 of 66 swollen joints, ≥6 of 68 tender joints, and either erythrocyte sedimentation rate (ESR) ≥28 mm/hour or a visual analogue scale (VAS) global health score ≥20mm).[3] Furthermore, patients from the BeSt study who received a comparable treatment with the IMPROVED study were selected: patients from arm 3 who started with combination therapy with prednisone. At baseline, the DAS<1.6 steered patients had a milder disease than DAS≤2.4 steered patients, they had lower DAS, shorter symptom duration and less joint damage. Disease activity and functional ability improved similarly during 5 years in the two targeted strategies. Despite differences in recruitment time and treatment, the different targets were achieved similarly in both studies, however more DAS<1.6 steered patients achieved DAS-remission and DFR. In the DAS<1.6 steered patients there was slightly less radiological damage progression after 1 and 5 years compared to the DAS≤2.4 steered patients. Functional ability over time was similar. Thus it seems that DAS<1.6 steered

treatment results in better outcomes in early active RA patients. However, a trial with exactly the same treatment comparing two different treatment targets is lacking. The next question is whether steering at a stricter treatment target like the ACR/EULAR Boolean remission criteria [31] will result in even better outcomes. On the one hand, this treatment target is difficult to achieve and can be influenced by other factors than inflammation caused by the disease itself. The question is whether all patients should be in strict remission or that a slight increase in disease activity is also acceptable.

As a next step, in **chapter 9** we focussed on whether adherence to these treatment protocols (DAS-remission (DAS<1.6) in the IMPROVED study and low disease activity (DAS≤2.4) in the BeSt study) is dependent on the target and whether both treatment protocols can be implemented in daily practice. Especially DAS-remission can be difficult to achieve in daily practice. Also, steering at a stricter target when disease activity is already low can lead to more costs and side effects without always having a clinical benefit. Furthermore, rheumatologists may not increase the medication if disease activity is already substantially decreased from baseline or when they think that the DAS is falsely high due to symptoms or inflammation not caused by rheumatoid disease activity. The willingness and arguments of the rheumatologist to treat-to-target and conditions that may result in non-adherece by the rheumatologists were investigated during 5 years follow up in both the IMPROVED and the BeSt study. We found that protocol adherence was higher in the DAS≤2.4 targeted study (86%) compared to the DAS<1.6 targeted study (70%). The COBRA study showed similar protocol violations.[32] In both studies protocol adherence decreased over time, but this was more distinct in the DAS<1.6 targeted study (from 100% to 48%) than in the DAS≤2.4 targeted study (100% to 72%). This was not particularly due to the required tapering of treatment if patients achieved DAS-remission, but against treatment intensification when the DAS was above the target. In the DAS≤2.4 targeted study, with more delayed tapering strategies, this was equal. In addition, protocol violations in both studies were associated with rheumatologists' disagreement with how the DAS represented actual disease activity, or with the next treatment step, and with a patient's VAS global health that was ≥20 mm higher than the rheumatologists VAS disease activity. In the DAS<1.6 targeted study also discrepancies between number of swollen and painful joints, measured ESR and VAS global health were associated with protocol violations. These outcomes suggest that a DAS steered treatment can be implemented in daily practice. The chance to achieve a predefined target is eventually high. A stricter treatment target is more difficult to implement in daily practice, because rheumatologists will be content with a slightly higher DAS if they think it does not represent actual disease activity. This may indicate that adherence to DAS steered protocols appear to depend at least in part on the height of the target, and in addition on how rheumatologists perceive that DAS reflects RA activity. Targeted treatment is important to achieve the best possible outcomes for RA patients. A stricter DAS target may not be achievable in all patients. Patient factors, type of disease, comorbidities,

and drug-related risks may affect components of the DAS or prevent further treatment adjustments. It would be preferable to combine the trend to set ever stricter treatment targets with the benefits of an individualized approach.

FUTURE PERSPECTIVES AND CONCLUSION

Data in this thesis suggest that early treatment with induction therapy followed by DAS-remission steered treatment in early RA patients and patients in an earlier phase before they are classified as rheumatoid arthritis is effective to gain good outcomes. Sustained DFR is achievable in approximately 26% of patients. It is important to figure out what the characterization is of these patients. If sustained DFR equals cure, does this mean that we have cured these patients? A proportion of the patients is temporarily in sustained DFR and can have a flare afterwards.

Our data suggest that there is still room to improve targeted treatment in RA in particular groups of patients. A proportion of the patients could not achieve DFR despite this effective treatment. This is a group of patients that deserve special attention. In the future research has to focus on this group of patients. What characterizes these patients? Can we find newer biomarkers to detect these patients in an earlier stage of the disease to treat them with an individualized treatment? The detection of new autoantibodies can give more insight in severity and response to medication to improve individualized treatment. This will prevent overtreatment and also effective treatment will be given at the right moment. ACPA positive and negative patients in the BeSt-study had similar outcomes, not indicating that both groups had to be treated in another way. New biomarkers may indicate a specific group of patients that may need other treatment.

Joint damage was one of the concerns when treating RA patients. Nowadays we do not see the extreme joint damage and deformations in RA patients. With early combination therapy joint damage can be prevented.[1,2] Some patients may have joint damage despite this treatment. It should be investigated what causes this joint damage in order to try to treat this persistent joint damage. Newer imaging techniques like magnetic resonance imaging (MR IMAGING) may detect changes in joints even before patients develop symptoms.

Induction therapy followed by targeted treatment is the optimal treatment strategy. A stricter target is associated with better outcomes, thus maybe the target should be even stricter than DAS-remission, for example Boolean remission. To date, a trial comparing different treatment targets is lacking. Boolean remission cannot be achieved if there is a slightly elevated tender joint count, swollen joint count, C-reactive protein or VAS global health. These components can also be higher due to other causes than rheumatoid activity, such as a simple cold or a pain syndrome. Therefore it can be difficult to achieve this target in patients and it can also

increase the risk of overtreatment of patients. Furthermore, physicians show less adherence to a strict treatment target. In the future tailor made individualized treatment targets varying over time in patients will be more acceptable. Taking into account differences between patients could result in the optimal treatment target. The optimal treatment and treatment target has to be further investigated. The rheumatologist has to keep in mind efficacy, side effects, costs and risk of over- or under treatment weighing these factors with knowledge from evidence based medicine. Clinical trials that compare different treatment strategies will help the rheumatologist in the future. New discovered biological DMARDs should be investigated in head to head clinical trials. It has to be elucidated whether it is worth to start a specific biological DMARD despite the high costs.

The main focus will change to detection of the disease in a more earlier stage than UA and treat the symptoms before the development of the disease. In the PROMPT (PRObable rheumatoid arthritis: Methotrexate versus Placebo Treatment) study in undifferentiated arthritis patients who were treated with MTX, although RA could not be prevented, the development to RA was delayed in ACPA-positive patients.[33] In ACPA-negative patients MTX showed no effect. In line with detecting the disease in an earlier stage the CSA (Clinically Suspect Arthralgia) study was set up including patients with arthralgia suspected to progress to arthritis according to their rheumatologist and investigated how many patients progress to arthritis. Approximately 11% progressed to arthritis a year later.[34] Recently, the TREAT EARLIER study was set up, treating clinically suspected arthralgia patients in this early stage. Clinically suspected arthralgia patients are randomized to MTX or placebo trying to prevent arthritis in these patients.

In conclusion, in patients with early RA and UA treatment with induction therapy followed by remission steered treatment results in a substantial number of patients achieving DAS-remission and sustained DFR, and prevention of joint damage. Although, this is not achieved in all patients. The focus will be on patients with poor outcomes despite this effective treatment. Individualized treatment should be furthermore investigated. Another focus will be to detect the disease earlier before symptoms occur and to treat before the development of the disease. Eventually to cure the disease, patients will be treated with combination therapy followed by an individualized treatment target.

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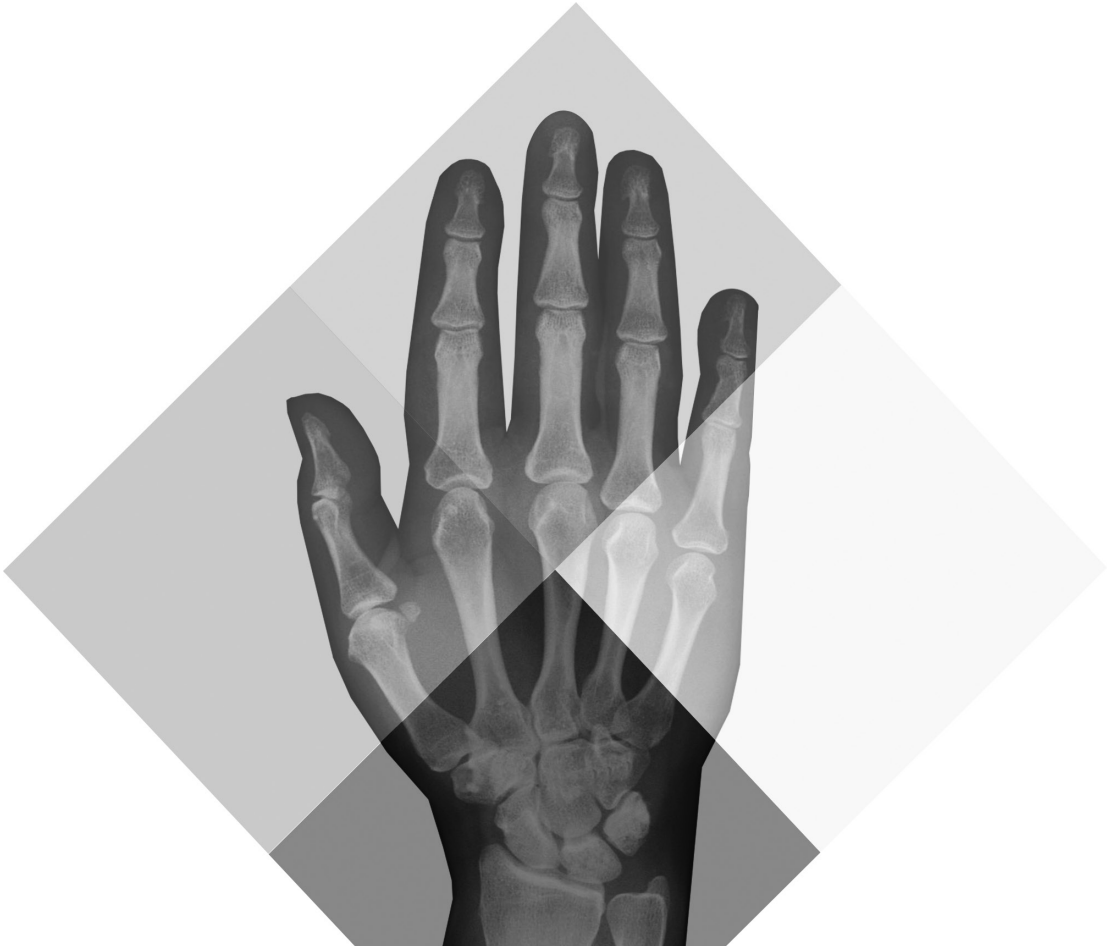
Chapter 11

NEDERLANDSE SAMENVATTING



REUMATOÏDE ARTRITIS

Reumatoïde artritis (RA) is een systemische auto-immuunziekte van onbekende etiologie, gekenmerkt door een chronische ontsteking van synoviale weefsel in gewrichten (artritis). De gewrichtsontsteking is typisch symmetrisch en meestal in de kleine gewrichten van de handen en voeten, echter andere gewrichten kunnen ook aangetast zijn. Patiënten presenteren zich met pijn, (ochtend) stijfheid en zwelling van het gewricht. Onbehandeld kan de ziekte leiden tot ernstige beschadiging van de gewrichten als gevolg van erosie van kraakbeen en bot, met bijkomende standsafwijkingen door het uitrekken van de pezen en ligamenten. Gewrichtsschade kan leiden tot verlies van fysiek functioneren, onvermogen om de dagelijkse taken van het leven uit te voeren en moeilijkheden bij het behouden van werk. Door vasculitis kunnen ook systemische effecten ontstaan, zoals interstitiële longziekte of cardiovasculaire ziekte. Eerdere studies hebben aangetoond dat patiënten baat hebben bij vroege behandeling. Het is daarom belangrijk om RA patiënten te diagnosticeren in een vroeg stadium. Met het oog daarop zijn de classificatiecriteria voor RA herzien in 2010, zodat patiënten in een eerder stadium van het ziekteproces worden geïdentificeerd. De nieuwe classificatiecriteria steunen voor een belangrijk deel op de aan- of afwezigheid van anti-gecitrullineerde proteïne antilichamen (ACPA), omdat ACPA vaker voorkomen bij vroege RA patiënten in vergelijking met patiënten met andere reumatische ziekten. Patiënten met artritis die niet kunnen worden geïdentificeerd als (manifestatie van) een specifieke reumatologische ziekten en/of niet aan de classificatiecriteria van een dergelijke ziekte voldoen, hebben ongedifferentieerde artritis (undifferentiated arthritis in het engels). Deze patiënten kunnen uiteindelijk RA krijgen of een andere chronische ontstekingsziekte of spontaan in remissie gaan. De PROMPT studie heeft laten zien dat behandeling met methotrexaat progressie naar RA vertraagde en niet kon voorkomen.

Aan de basis van dit proefschrift is ons doel om de resultaten van patiënten met reumatoïde artritis of ongedifferentieerde artritis te verbeteren. Uit onderzoek in de afgelopen decennia is gebleken dat RA patiënten zo snel mogelijk behandeld moeten worden en dat de optimale behandeling om snelle verbetering te krijgen combinatietherapie met corticosteroïden of een biologische DMARD is, bij onvoldoende respons gevolgd door een treat-to-target regime. Behandeling gericht op DAS-remissie (DAS<1,6), of ten minste lage ziekte activiteit (DAS≤2,4), is aanbevolen om klinische verslechtering en onomkeerbare schade door ontstekingen te voorkomen. Als remissie wordt bereikt, kan medicatie worden afgebouwd en indien remissie vroeg wordt bereikt binnen een zogenaamde “window of opportunity”, is het mogelijk dat chronische ontsteking geheel wordt voorkomen en langdurige medicatievrije remissie wordt bereikt. Om dit te onderzoeken werd de IMPROVED studie ontworpen. Data over de 5 jaar uitkomsten en mogelijke bezwaren tegen verdere implementatie van de resultaten, werden

in hoofdstuk 4 van dit proefschrift besproken. Andere hoofdstukken zijn gericht op mogelijk verdere verbeteringen voor patiënten met bepaalde reumatische aandoeningen, zoals auto-antilichaam negatieve RA, waar er minder risico op gewrichtsschade is en een onzekerheid over de beste behandelingsstrategie, en chronische monoartritis van de knie, waarbij lokale behandeling de voorkeur heeft, maar de optimale medicatie niet duidelijk is. In dit hoofdstuk zal de inhoud van dit proefschrift worden samengevat en bediscussieerd.

DE IMPROVED STUDIE

De IMPROVED studie is de eerste behandel strategie studie om vroege (≤2 jaar) RA op basis van de herziene classificatie criteria (ziekte in een vroegere fase) en ongedifferentieerde artritis (niet-geclassificeerde artritis, maar klinisch verdacht voor RA) patiënten te behandeling gericht op het behalen van vroege medicatievrije remissie. Alle patiënten begonnen met een intensieve inductie therapie (methotrexaat (MTX) en prednison in een hoge dosis afgebouwd tot een lage dosis in 7 weken) in de eerste 4 maanden gevolgd door DAS-remissie (DAS<1,6) gestuurde behandeling elke 4 maanden, gevolgd gedurende 5 jaar. Deze behandeling resulteerde in het bereiken van DAS-remissie bij 61% van de patiënten na 4 maanden behandeling. Patiënten die DAS-remissie op 4 maanden bereikten, konden de medicatie stapsgewijs afbouwen, totdat medicatievrije remissie kon worden bereikt op 1 jaar na start van de behandeling. Verlies van DAS-remissie vereiste herstart van de laatste effectieve behandeling. Patiënten die niet op 4 maanden DAS-remissie bereikten werden gerandomiseerd in arm 1: DMARD (antirheumatische medicatie) combinatietherapie (MTX, hydroxychloroquine en sulfasalazine) met prednison of arm 2: MTX plus adalimumab. Na 4 maanden verbeterde het fysiek functioneren in alle patiënten. In de vroege DAS-remissie groep werd met de HAQ vragenlijst vrijwel normaal fysiek functioneren gemeten, maar in de andere groepen bleef het functioneren iets minder goed. Na 1 jaar was DAS-remissie bereikt door 54% van de patiënten en 21% van de patiënten waren in medicatievrije remissie. Na 2 jaar was 49% van de patiënten in DAS-remissie en 21% in medicatievrije remissie (hoofdstuk 2). Na 5 jaar waren deze percentages vergelijkbaar: 48% was in DAS-remissie en 22% in medicatievrije remissie (hoofdstuk 4). Ongedifferentieerd artritis patiënten hadden reeds een mildere ziekte op baseline vergeleken met de RA patiënten en minder autoantilichaam positiviteit. Toch waren percentages DAS-remissie vergelijkbaar gedurende 5 jaar bij RA en ongedifferentieerde artiritis patiënten. Maar ongedifferentieerde artiritis patiënten behaalden meer medicatievrije remissie dan RA patiënten, op 1 jaar (30% versus 19%), op 2 jaar (34% versus 19% , hoofdstuk 2) en op 5 jaar (33% versus 19%, hoofdstuk 4). Ook autoantilichaam (reumatoïde factor (RF) en ACPA) negatieve patiënten bereikten vaker medicatievrije remissie, wat aangeeft dat ze een mildere ziekte hadden. Dit suggereert dat ongedifferentieerde

artritis patiënten in een vroegere, nog niet chronische fase van de ziekte waren of dat zij en autoantilichaam negatieve patiënten spontaan in remissie zouden gaan.

Zoals gezegd hadden patiënten die vroeg DAS-remissie op 4 maanden bereikten een beter fysiek functioneren en bereikten zij vaker DAS-remissie en medicatievrije remissie dan patiënten die niet vroege DAS-remissie bereikten op 4 maanden en die dus gerandomiseerde moesten worden. Patiënten die vroege DAS-remissie bereikten hadden al op baseline een mildere ziekte. De mate van daling in DAS en HAQ was gelijk bij alle patiënten. Dit suggereert dat patiënten die beginnen met een mildere ziekte betere resultaten bereiken door de lagere beginwaarden, niet vanwege een sterkere verbetering. De meerderheid van de patiënten (75%) die werden gerandomiseerd in arm 1 hadden onvoldoende of slechts tijdelijk verbetering op de eerste behandelstap (of herstart na aanvankelijk afbouwen) met DMARD combinatietherapie. Zij kregen alsnog adalimumab met MTX, de eerste behandelstap in arm 2. Er waren ook 50 patiënten die niet in DAS-remissie waren op 4 maanden, zij werden niet gerandomiseerd volgens het protocol, omdat er discrepantie was tussen de DAS gemeten door de onderzoeks verpleegkundige en de DAS gemeten door de reumatoloog. Deze patiënten werden behandeld naar inzicht van de reumatoloog, welke ook een treat-to-target strategie aanhield. Deze patiënten toonden vergelijkbare resultaten als de gerandomiseerde patiënten.

GEWRICHTSSCHADE

Inductietherapie gevolgd door DAS-remissie gestuurde behandeling resulteert in minimale gewrichtsschade in de meeste RA en UA patiënten na 2 jaar (hoofdstuk 2). Slechts 8% (50/610) van de patiënten vertoonden progressie op röngenfoto's van handen en voeten. Ook na 5 jaar werd gewrichtsschade goed onderdrukt (hoofdstuk 4). Ongedifferentieerde artritis patiënten en auto-antilichaam negatieve patiënten hadden het minst gewrichtsschadeprogressie. In vergelijking met andere studies hadden patiënten in de IMPROVED studie minder gewrichtsschadeprogressie. In deze groep patiënten waarbij de ziekte activiteit over het algemeen laag was en de gezamenlijke schade minimaal was, kan het informatief zijn om te kijken naar welke factoren samenhangen met en mogelijk bijdragen aan gewrichtsschadeprogressie bij deze patiënten ongeacht (onderdrukking van) ontsteking. We hebben gekeken naar factoren die kunnen voorspellen wie na 2 jaar radiologische progressie heeft en vonden dat leeftijd en autoantilichaam positiviteit (combinatie van ACPA en anti-gecarbamyleerd eiwit antilichamen (anti-CarP)) geassocieerd waren met radiologische progressie (hoofdstuk 3). Gewrichtsschade werd voornamelijk veroorzaakt door de progressie in gewrichtsspleetvernauwing in plaats van progressie van erosies bij

deze patiënten. Een mogelijke verklaring zou kunnen zijn dat naar mate de leeftijd stijgt, dit kan leiden tot primair handartrose, waarbij ook gewrichtsspleetvernauwing optreedt. Het is bekend dat autoantilichaam positiviteit geassocieerd is met ernstige ziekte en meer gewrichtsschade. Autoantilichaam positiviteit kan een fenotype met een bijzonder slechte prognose vertegenwoordigen. Het vinden van voorspellende factoren bij RA en UA patiënten met minimale schadeprogressie, zal alleen relevant zijn voor het begrip van RA fenotypen, omdat minimale schadeprogressie niet relevant zal zijn in de klinische praktijk.

In een andere studie (de BeSt studie) hebben we ons gericht op de gewrichtsspleetvernauwing en schadeprogressie in verschillende leeftijdsgroepen (hoofdstuk 7). De BeSt studie is een multicenter, gerandomiseerd klinisch onderzoek in patiënten met recent ontstane, actieve RA. De patiënten werden bij aanvang van behandeling gerandomiseerd in 4 therapeutische strategieën, waarin de volgorde van behandeling werd afgestemd op het meten van de ziekte activiteit (DAS), die ≤2,4 moest zijn. Bij hogere DAS werd de medicatie geïntensiveerd, bij aanhoudend lage DAS werd medicatie afgebouwd. De DAS werd elke 3 maanden gemeten. Onze hypothese was dat progressie in gewrichtsspleetvernauwing en voorspellers van gewrichtsspleetvernauwing kunnen verschillen tussen de verschillende leeftijdsgroepen, als dit wordt verklaard door primaire artrose, een aandoening die vaker voorkomt naarmate de leeftijd stijgt. Leeftijdspecifieke risicofactoren voor de ontwikkeling van gewrichtsspleetvernauwing werden vergeleken in 3 leeftijdsgroepen (≤40, >40 - ≤55 en ≥55). Oudere RA patiënten (≥55 jaar) toonde vaker en ernstiger gewrichtsspleetvernauwing op baseline dan jongere patiënten. Oudere patiënten hadden een hogere BSE en hogere erosiescores wat reumatische ontsteking aangeeft in vergelijking met jongere patiënten die meer gezwollen gewrichten hadden. Na 10 jaar follow-up was er geen verschil in gewrichtsspleetvernauwing tussen de leeftijdsgroepen, maar de patiënten ≤40 jaar hadden meer toename van gewrichtsspleetvernauwing. Risicofactoren voor gewrichtsspleetvernauwing waren iets anders tussen de leeftijdsgroepen. Bij patiënten ≥55 jaar waren autoantilichamen en een hoge BSE onafhankelijk geassocieerd met gewrichtsspleetvernauwing progressie na 10 jaar. In de >40 ≤55 jaar leeftijdscategorie waren er geen onafhankelijke voorspellers van gewrichtsspleetvernauwing progressie. In de <40 jaar leeftijdsgroep waren onderdelen van de DAS die ontsteking aangeven (gezwollen gewrichten en BSE over de loop van tijd) onafhankelijk geassocieerd. In de oudere leeftijdsgroepen kan primaire artrose hebben geleid tot gewrichsspleetvernauwing. Dit kan een effect hebben op hoe radiologische scoremethodes kunnen worden geïnterpreteerd om effecten van behandeling bij verschillende leeftijdsgroepen te verklaren.

INTRA-ARTICULAIRE INJECTIES

Geïsoleerde monoartritis kan worden behandeld met een intra-articulaire injectie met corticosteroïden, maar er is een hoog recidief kans en her-injectie kan niet onbeperkt worden gegeven in hetzelfde gewricht. Als alternatief kunnen intra-articulaire injecties met een TNF-remmer worden geprobeerd, maar studies tonen aan dat dit niet klinisch superieur is aan intra-articulaire injecties met corticosteroïden. Om te onderzoeken of er op beeldvorming een mogelijke verklaring kan worden gevonden voor de teleurstellende klinische resultaten van een intra-articulaire injectie in een ontstoken knie, is de RIA (Remicade Intra Articularly) studie opgezet, een dubbelblind gerandomiseerd onderzoek bij patiënten met chronische gonartritis met verschillende onderliggende ziekten die persisteerden of recidiveerden na eerder intra-articulaire behandeling met corticosteroïden. Er werden voor- en na-injectie afbeelden gemaakt m.b.v. magnetic resonance (MR) imaging. MRI bevindingen correleren goed met histologische bevindingen. De patiënten werden gerandomiseerd in een groep die behandeld werd met intra-articulaire infliximab (een tumor necrose factor α blokker) en een groep die behandeld werd met intra-articulaire methylprednisolon. De klinische resultaten na 6 maanden toonden aan dat infliximab niet superieur was t.o.v. prednisolon. Alle patiënten die infliximab hadden kregen hadden persisterende of recidiverende gonartritis na 6 maanden, terwijl 6 van de 13 initiële injecties met methylprednisolon na 6 maanden nog aanhoudend effect hadden waren. Onze hypothese was dat ofwel voor de behandeling de hoeveelheid ontsteking te hoog was om (permanent) te verbeteren na lokale injectie ofwel dat aanvankelijke verbetering is opgetreden maar dat aanhoudende ziekteprocessen hebben geleid tot een recidief van ontsteking. In hoofdstuk 5 hebben we ons gericht op pre-injectie MR scores en veranderingen in MR scores na behandeling met hetzij intra-articulaire injecties met infliximab of methylprednisolon in relatie tot klinisch respons. We vonden voor injectie vergelijkbare ontstekingsverschijnselen op MR in de beide behandelgroepen. Er was een vermindering van ontsteking en effusie na 4 weken zowel in knieën behandeld met intra-articulaire infliximab als in knieën behandeld met i.a. methylprednisolon. In infliximab geïnjecteerde knieën was de vermindering aanzienlijk, in vergelijking met methylprednisolon geïnjecteerd knieën. De vermindering werd in verband gebracht met een vroege klinische respons, gemeten met een klinisch kniegewrichtsscore (knie pijn (0-3), knie zwelling (0-3) en knie pijn van de patiënt (0-1)). Echter, na 6 maanden was er geen verband meer tussen de klinische score, de MR scores of veranderingen in de MR scores. Alle infliximab geïnjecteerd knieën hadden een recidief en dit was 50% in methylprednisolon geïnjecteerd knieën. Een recidief was niet geassocieerd met specifieke MR veranderingen. Methylprednisolon geïnjecteerd knieën die vroege klinische verbetering vertonen, hadden minder vaak een recidief na 6 maanden. Een verklaring voor dit verschil kan zijn de verschillende werkingsmechanismen van de twee medicijnen.

ACPA-NEGATIEVE RA

Onderzoek richt zich vooral op de aanwezigheid van ACPA, omdat dit resulteert in een ernstige ziekte bij RA patiënten, met meer gewrichtsschade en minder kans op medicatievrije remissie. Het omgekeerde hiervan werd ook gezien in hoofdstuk 2 en 4, waar ACPA-negatieve RA en ongedifferentieerde artritis patiënten minder gewrichtsschadeprogressie hadden en meer medicatievrije remissie behaalden dan ACPA-negatieve patiënten. ACPA-negatieve RA is misschien een andere ziekte entiteit dan ACPA-positieve RA en zou daarom op een andere manier behandeld moeten worden. Echter wat deze behandeling zou moeten zijn, moet nog verduidelijkt worden. Er wordt gesuggereerd dat ACPA-negatieve RA geen intensieve behandeling nodig zou hebben, omdat ACPA-negatieve RA patiënten minder kans hebben om gewrichtsschade te ontwikkelen en meer kans hebben om medicatievrije remissie te bereiken. In een subanalyse van de BeSt studie (hoofdstuk 6) hebben we onderzocht welke initiële behandelstrategie effectiever is in ACPA-negatieve RA patiënten. Initiële combinatietherapie was effectiever, met eerdere functionele verbetering dan bij initiële monotherapie, zonder bijkomende bijwerkingen. Een derde van de ACPA-negatieve patiënten kon de initiële combinatietherapie na 1 jaar afbouwen naar monotherapie. Patiënten die faalden op MTX monotherapie reageerden ook minder goed op de tweede stap met sulfasalazine. Gedurende 10 jaar van doelgerichte therapie was er geen verschil tussen de uitkomsten tussen combinatietherapie en monotherapie en schadeprogressie was laag in beide behandelingsgroepen. In vroege actieve RA patiënten moet initiële behandeling gericht zijn op snelle verlichting van de symptomen en er is geen reden om de eerste behandelkeuze te overwegen op basis van de ACPA status.

BEHANDEL DOEL

Initiële combinatietherapie, gevolgd door een treat-to-target strategie is de optimale behandelingsstrategie om ziekte activiteit te onderdrukken in vroege artritis patiënten. Het optimale behandeldoel staat ter discussie. Aanbevelingen stellen dat de behandeling moet worden gestuurd op het bereiken van remissie (DAS<1,6) of op zijn minst lage ziekte activiteit (DAS≤2,4). In hoofdstuk 8 onderzoeken we welk van de twee ‘targets’ het beste is. We hadden twee klinische onderzoeken tot onze beschikking, uitgevoerd in dezelfde ziekenhuizen, in vroege RA patiënten die werden behandeld met een treat-to-target strategie, maar elk gericht zijn een ander behandeldoel. De BeSt studie ging van start in 2000 en introduceerde behandeling gericht op lage ziekte activiteit (DAS≤2,4), gemeten met intervallen van 3 maanden. De IMPROVED studie begon 7 jaar later gericht op DAS-remissie (DAS<1,6), gemeten met intervallen van 4 maanden. Om de patiënten van 2 verschillende studies te

kunnen vergelijken hebben we patiënten geselecteerd die vergelijkbaar waren: vroege actieve RA-patiënten van de IMPROVED studie die voldeden aan de 1987 classificatiecriteria voor RA en op basis van de mate van ziekte activiteit op baseline aan de inclusiecriteria van de BeSt studie zouden hebben voldaan (≤2 jaar klachtduur, ≥6 van 66 gezwollen gewrichten, ≥6 van 68 pijnlijke gewrichten, en ofwel bezinking (BSE) ≥28 mm/uur of een visuele analoge schaal (VAS) algemeen welbevinden score ≥20mm). Verder werden patiënten uit de BeSt studie geselecteerd die een vergelijkbare behandeling hadden gehad als in de IMPROVED studie: patiënten uit arm 3 die zijn begonnen met combinatietherapie met MTX en prednison (en sulfasalazine). Op baseline hadden de DAS<1,6 gestuurde patiënten een mildere ziekte dan DAS≤2,4 gestuurd patiënten, ze hadden een lagere DAS, kortere klachtduur en minder gewrichtsschade. Ziekte activiteit en fysiek functioneren verbeterden in gelijke mate gedurende 5 jaar in de twee doelgerichte strategie studies. Ondanks verschillen in wervingstijd en behandeling werden de behandeldoelen in beide studies even vaak gerealiseerd, echter meer DAS<1,6 gestuurde patiënten bereikten DAS-remissie en medicatievrije remissie. In de DAS<1,6 gestuurde patiënten was er iets minder radiologische schade progressie na 1 en 5 jaar vergeleken met de DAS≤2,4 gestuurde patiënten. Fysiek functioneren was na verloop van tijd vergelijkbaar. Het lijkt er dus op dat DAS<1,6 gestuurde behandeling leidt tot betere resultaten in vroege actieve RA patiënten. Echter, een onderzoek waarin precies dezelfde behandeling vergeleken wordt met twee verschillende behandel doelen ontbreekt. De volgende vraag is of het sturen op een strengere behandeldoel, zoals de ACR/EULAR Boolean remissiecriteria, zal resulteren in nog betere resultaten. Dit behandeldoel is relatief moeilijk te bereiken, ook omdat wel of niet voldoen aan de criteria kan worden beïnvloed door andere factoren dan de ontsteking veroorzaakt door de ziekte zelf. De vraag is of alle patiënten zo'n strenge remissie moeten bereiken, of dat een iets hogere grens van de ziekte activiteit eveneens aanvaardbaar is.

Als een volgende stap, in hoofdstuk 9 hebben we ons gericht op de vraag of de naleving van deze behandelprotocollen (DAS-remissie (DAS<1.6) in de IMPROVED studie en lage ziekte activiteit (DAS≤2,4) in de BeSt studie) afhankelijk is van het behandeldoel en of beide behandelprotocollen in de dagelijkse praktijk kunnen worden uitgevoerd. Vooral DAS-remissie kan moeilijk te bereiken zijn in de dagelijkse praktijk. Ook het sturen op een strenger doel door medicatie te intensiveren wanneer de ziekte activiteit al laag is kan leiden tot meer kosten en bijwerkingen zonder altijd een klinisch voordeel. Bovendien kunnen reumatologen kiezen om niet de medicatie verhogen als de ziekte activiteit al aanzienlijk gedaald is t.o.v. baseline, of wanneer ze denken dat de DAS ten onrechte hoog is als gevolg van symptomen of ontsteking die niet veroorzaakt wordt door reumatoïde artritis ziekte activiteit. De bereidheid en argumenten van de reumatologen om treat-to-target toe te passen en omstandigheden die kunnen leiden tot het niet naleven van de protocollen door de reumatologen werden onderzocht gedurende

5 jaar in de IMPROVED en de BeSt studie. We vonden dat protocolnaleving hoger was in de DAS≤2,4 gestuurde studie (86%) dan in de DAS<1,6 gestuurde studie (70%). De COBRA studie toonde een vergelijkbare percentage (24%) in niet-naleving van het protocol. In beide studies daalde de protocolnaleving na verloop van tijd, maar dit was meer uitgesproken in de DAS<1,6 gestuurde studie (van 100% naar 48%) dan in de DAS≤2,4 gestuurde studie (van 100% naar 72%). Dit was in de DAS<1,6 gestuurde studie met name niet vanwege het vereiste snelle afbouwen van medicatie als patiënten DAS-remissie bereikten, maar betrof vooral ten onrechte niet intensiveren van behandeling wanneer de DAS boven het behandeldoel was. In de DAS≤2,4 gestuurde studie, waar afbouw van medicatie in een langzamer tempo werd voorgeschreven, betrof niet-naleving van het protocol even vaak onterecht niet-intensiveren als onterecht niet-afbouwen. Daarnaast was niet-naleving van het protocol in beide studies geassocieerd met oneensheid van de reumatoloog met hoe de DAS de eigenlijke ziekte activiteit vertegenwoordigt, oneensheid met de volgende behandel stap, en met een situatie waarin de patiënt de ziekte activiteit hoger inschatte dan de arts. In de DAS<1,6 gerichte studie waren er ook discrepanties tussen het aantal gezwollen en pijnlijke gewrichten, gemeten BSE en VAS algemeen welbevinden die geassocieerd waren met het niet-naleven van het protocol. Deze resultaten suggereren dat een DAS-gestuurde behandeling in de dagelijkse praktijk kan worden uitgevoerd. De kans om een vooraf gedefinieerde doel te bereiken is uiteindelijk hoog. Een strengere behandelingdoel is moeilijker te implementeren in de dagelijkse praktijk, omdat reumatologen ook tevreden zullen zijn met een iets hogere DAS als ze denken dat het niet de werkelijke ziekte activiteit vertegenwoordigd. Dit kan erop wijzen dat naleving van DAS gestuurde protocollen afhankelijk kan zijn, ten minste gedeeltelijk, van de hoogte van de DAS als behandeldoel, en bovendien van hoe reumatologen zien dat DAS RA activiteit weerspiegelt. Gerichte behandeling is belangrijk om de best mogelijke resultaten te behalen in RA patiënten. Een strenger DAS behandeldoel kan niet haalbaar zijn in alle patiënten. Patiëntfactoren, type ziekte, comorbiditeit, en medicatiegerelateerde risico's kunnen onderdelen van de DAS beïnvloeden of verdere behandelingaanpassingen voorkomen. Het verdient de voorkeur om de trend te combineren naar steeds strengere behandeldoelstellingen met de voordelen van een individuele benadering.

TOEKOMSTPERSPECTIEVEN EN CONCLUSIE

Data in dit proefschrift suggereren dat vroege behandeling met inductietherapie gevolgd door DAS-remissie gestuurde behandeling in vroege RA patiënten en patiënten in een eerdere fase voordat ze worden geclassificeerd als reumatoïde artritis effectief is om goede resultaten te krijgen. Aanhoudende medicatievrije remissie is haalbaar bij ongeveer 26% van de patiënten. Het is belangrijk om erachter te komen wat de kenmerken zijn van deze patiënten.

Als aanhoudende medicatievrije remissie gelijk is aan genezing, betekent dit dat we deze patiënten hebben genezen? Een deel van de patiënten is tijdelijk in medicatievrije remissie en kan later een opvlamming van de ziekte krijgen.

Onze resultaten suggereren dat er nog ruimte is om gerichte behandeling in RA te verbeteren in bepaalde groepen patiënten. Een deel van de patiënten kon niet medicatievrije remissie bereiken ondanks deze effectieve behandeling. Dit is een groep patiënten die speciale aandacht verdient. In de toekomst moet het onderzoek zich richten op deze groep patiënten. Wat kenmerkt deze patiënten? Kunnen we nieuwere biomarkers vinden om deze patiënten op te sporen in een eerder stadium van de ziekte om ze te kunnen behandelen met een geïndividualiseerde behandeling? De detectie van nieuwe autoantilichamen kan meer inzicht geven in de ernst en de respons op medicatie om geïndividualiseerde behandeling te verbeteren. Dit zal overbehandeling voorkomen en tevens ervoor zorgen dat efficiënte behandeling op het juiste moment gegeven gaat worden. ACPA-positieve en negatieve patiënten in de BeSt studie hadden vergelijkbare resultaten, wat aangeeft dat beide groepen niet op een andere manier behandeld moeten worden. Nieuwe biomarkers kunnen een specifieke groep patiënten aanwijzen die andere behandeling nodig hebben.

Gewrichtsschade was een van de zorgen bij de behandeling van RA patiënten. Tegenwoordig zien we niet de extreme gewrichtsschade en vervormingen bij RA patiënten. Met vroege combinatietherapie kan gewrichtsschade worden voorkomen. Sommige patiënten kunnen gewrichtsschade hebben ondanks deze behandeling. Er moet worden onderzocht wat de oorzaken van deze gewrichtsschade zijn om deze hardnekkige gewrichtsschade te proberen te behandelen. Nieuwere beeldvormende technieken zoals MR imaging kunnen veranderingen in de gewrichten op sporen voordat patiënten symptomen ontwikkelen.

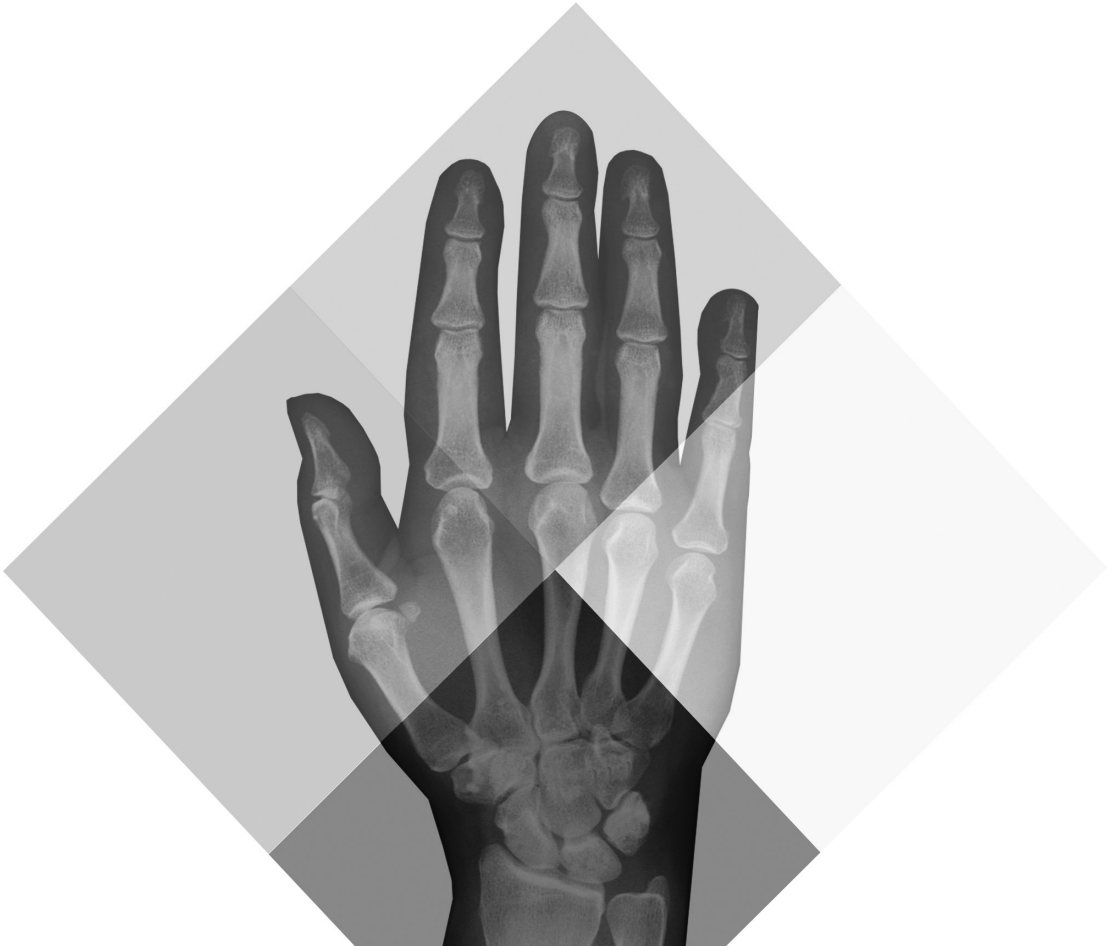
Inductietherapie gevolgd door gerichte behandeling is de optimale behandelingsstrategie. Een strikter behandeldoel wordt geassocieerd met betere resultaten, dus misschien moet het behandeldoel nog strenger worden dan DAS-remissie, bijvoorbeeld Boolean remissie. Tot op heden ontbreekt er een onderzoek waarin verschillende behandel doelen worden vergeleken. Boolean remissie kan niet worden bereikt als er licht verhoogde pijnlijke gewrichten, gezwollen gewrichten, C-reactief proteïne of VAS algemeen welbevinden is. Deze componenten kunnen ook hoger zijn als gevolg van andere oorzaken dan reumatoïde activiteit zoals een verkoudheid of een pijnsyndroom. Daarom kan het moeilijk zijn om dit doel te bereiken in patiënten en het kan ook het risico van overbehandeling verhogen. Bovendien houden artsen zich minder aan een strengere behandeldoel. In de toekomst zal een op maat gemaakt geïndividualiseerd behandeldoel variërenend in de tijd voor patiënten meer aanvaardbaar zijn. Rekening houdend met verschillen tussen patiënten kan dit leiden

tot het optimale behandeldoel. De optimale behandeling en het optimale behandeldoel moeten verder worden onderzocht. De reumatoloog moet de werkzaamheid, bijwerkingen, kosten en risico's van over- of onder behandeling in gedachten houden en deze factoren afwegen met kennis van evidence-based medicine. Klinische onderzoeken die verschillende behandelingsstrategieën met elkaar vergelijken zullen de reumatoloog in de toekomst helpen. Nieuw ontdekte biologische DMARD's moeten worden onderzocht in head to head klinische onderzoeken. Er dient te worden opgehelderd of het de moeite waard is om een specifieke biologische DMARD te starten ondanks de hoge kosten.

De aandacht zal verschuiven naar de detectie van de ziekte in een vroeger stadium dan ongedifferentieerde artritis en behandeling van de symptomen vóór de ontwikkeling van de ziekte. In de PROMPT studie werden ongedifferentieerde artritis patiënten behandeld met MTX. Hoewel RA niet kon worden voorkomen, werd de ontwikkeling naar RA vertraagd in ACPA-positieve patiënten. In ACPA-negatieve patiënten toonde MTX geen effect. In lijn met het opsporen van de ziekte in een eerder stadium werd de CSA studie opgezet, met patiënten met gewrichtspijn die volgens hun reumatoloog deed vermoeden dat artritis zou ontwikkelen. Er werd onderzocht hoeveel patiënten artritis ontwikkelen. Ongeveer 11% ontwikkelde artritis een jaar later. Patiënten bij wie op een MRI tekenen van ontsteking werden gezien hadden de grootste kans. Onlangs is de TREAT EARLIER studie opgezet, om te onderzoeken of in dit vroege stadium behandeling kan voorkómen dat artritis optreedt. Klinisch verdachte artralgie patiënten worden na randomisatie in een dubbelblind onderzoek behandeld met MTX of placebo. Indien niet alleen tijdens, maar ook na staken van de behandeling geen artritis optreedt, zal de eerste stap zijn gezet naar preventieve behandeling van RA, en zijn we op weg om deze ernstige ziekte werkelijk de wereld uit te helpen.

Appendix

CURRICULUM VITAE
LIST OF PUBLICATIONS
DANKWOORD



CURRICULUM VITAE

Gülşah is geboren op 19 augustus 1985 in Alphen aan den Rijn. Na het behalen van haar VWO diploma aan het Groene Hart Lyceum in Alphen aan den Rijn begon zij in 2003 met de studie rechtsgeleerdheid aan de Universiteit van Leiden. Na het behalen van haar bachelor diploma stapte zij in 2006 over naar de studie geneeskunde in Leiden. In 2012 legde zij het artsexamen af, waarna zij begon als arts-onderzoeker op de afdeling reumatologie van het Leids Universitair Medisch Centrum. Onder begeleiding van mw. dr. C.F. Allaart en prof. dr. T.W.J. Huizinga werkte zij aan het onderzoek beschreven in dit proefschrift. Tijdens haar onderzoeksperiode won zij de ‘EULAR Abstract Award in Clinical Science 2016’.

In september 2016 is zij begonnen aan de opleiding tot reumatoloog in het LUMC (opleider: prof. dr. T.W.J. Huizinga). Momenteel volgt zij de vooropleiding interne geneeskunde in het Alrijne Ziekenhuis te Leiderdorp (opleider: dr. S. Anten).

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