Treat to target in rheumatoid arthritis: opportunities and outcomes

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TREAT TO TARGET IN RHEUMATOID ARTHRITIS: OPPORTUNITIES AND OUTCOMES

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CONTENTS

Chapter 1	General introduction	7
Chapter 2	Early local swelling and tenderness are independent predictors of large joint damage after 8 years of DAS steered treatment in recent onset RA patients	21
Chapter 3	Large joint damage in patients with early rheumatoid arthritis and its association with treatment strategy and damage of the small joints	33
Chapter 4	Rapid radiological progression in the first year of early RA is predictive of disability and joint damage progression during 8 years of follow-up	47
Chapter 5	The association of treatment response and joint damage with ACPA status in recent onset RA: a subanalysis of the 8-year follow-up of the BeSt study	57
Chapter 6	The association between body mass index and treatment response in recent onset RA	69
Chapter 7	Discontinuation of infliximab and potential predictors of persistent low disease activity in patients with early rheumatoid arthritis and DAS steered therapy: subanalysis of the BeSt study	83
Chapter 8	Do we need guidelines to stop as well as to start biological therapies?	99
Chapter 9	Drug-free remission: is it already possible?	113
Chapter 10	Is achieving remission associated with better health related quality of life than maintaining low disease activity in rheumatoid arthritis patients?	127
Chapter 11	Summary and discussion	139
Chapter 12	Nederlandse samenvatting	153
Appendix	Role of the funding source	165
	Acknowledgements	168
	Author affiliations	169
	Curriculum Vitae	170
	List of publications	171
	Dankwoord	173

Chapter 1

General introduction

Section adapted from:
BeSt practice: the success of early-targeted treatment in rheumatoid arthritis

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RHEUMATOID ARTHRITIS

Rheumatoid arthritis is a systemic auto-immune disease with a prevalence of 0.5-1% in developed countries.[1] In patients with RA, the overproduction of tumor necrosis factor alpha (TNFα) leads to production of other pro-inflammatory cytokines and to joint inflammation and joint destruction. Both active inflammation and joint destruction in small and large joints can lead to functional disability. It is unknown whether in new RA patients in whom active inflammation is rapidly suppressed, good functional ability can be maintained over time. Especially as large joint damage is an important contributor to functional disability and this is often reported to occur later in the disease course than small joint damage, prevention of large joint damage could be beneficial for the maintenance of good functional ability.[2] Prolonged inflammation is associated with extra-articular disease and co-morbidity such as cardiovascular disease.[1]
In 1987, classification criteria were developed to separate rheumatoid arthritis from other inflammatory disorders.[3](*figure 1*) A limitation of these criteria is that they are suitable to identify patients with established RA, but less so for patients with early arthritis. As evidence for the benefits of treating RA early accumulated, new criteria were proposed

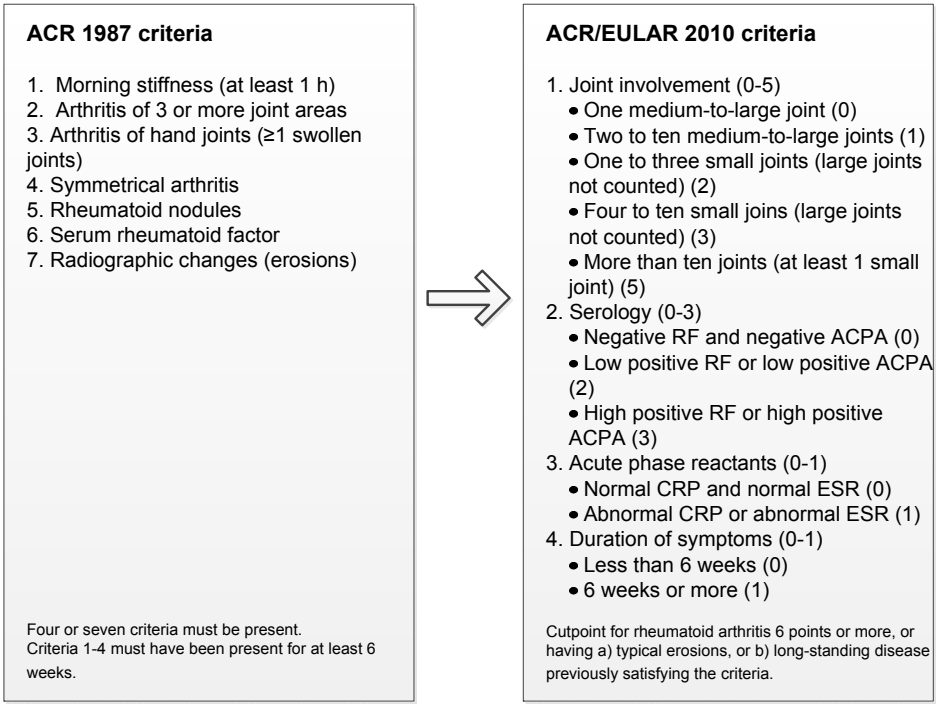

Figure 1: ACR 1987 and ACR/EULAR 2010 rheumatoid arthritis classification criteria, adapted from Scott *et al.*[1]

in 2010 to enable earlier diagnosis of RA.[4] Aiming to combine greater sensitivity with sufficient specificity, presence of anti-citrullinated protein antibodies was added to the criteria, as this is a strong indicator that early arthritis may be early rheumatoid arthritis.

ANTI-CITRULLINATED PROTEIN ANTIBODIES (ACPA)

Even more so than auto-antibody rheumatoid factor (RF), anti-citrullinated protein antibodies (ACPA) are highly specific for rheumatoid arthritis. These are antibodies directed to citrulline-containing epitopes and can be detected using the CCP2 test.[5] Citrulline is generated by post-translational modification of arginine by peptidylarginine deaminase. ACPA can be found years before the diagnosis of RA is made.[6] It has been suggested that ACPA play a role in both the process of developing RA as well as the chronicity of the disease.[7] In patients in whom the diagnosis of RA is made, presence of ACPA has been shown to be predictive of a less favorable disease course, with higher disease activity, more functional disability and more joint damage progression.[8-14] Possibly, ACPA-positive patients need early combination treatment, and/or a more stringent treatment goal is necessary. The disease course and disease outcomes may be so different that it has been suggested that ACPA-positive and ACPA-negative RA are two different diseases.[15,16] This hypothesis is supported by the finding that a genetic marker, the presence of the human leukocyte antigen shared epitope allele, only predisposes to ACPA-positive and not to ACPA-negative RA.[17]

TREATMENT - DISEASE MODIFYING ANTI-RHEUMATIC DRUGS (DMARD)

In the last 3 decades, the approach to treatment of RA has changed from gradual escalation of therapy starting with non-steroid anti-inflammatory drugs (NSAIDs), to early introduction of a DMARD as monotherapy or in combination with a corticosteroid.[18] Methotrexate is generally considered the anchor drug for the treatment of RA.[19] As for other DMARD, methotrexate's working mechanism is incompletely understood. If methotrexate is contraindicated or not tolerated, sulfasalazine or leflunomide are often second choice.[20] It has been shown however that it is unlikely that the disease will be significantly suppressed if such therapies are tried after methotrexate has already proved to be ineffective.[21] Prolonged disease activity may in these patients be prevented if a biologic anti-rheumatic agent is introduced.

Treatment - Biological agents

In the 1990s, the first biologic anti-rheumatic agent, a TNFα-blocker, was introduced for patients who had failed on synthetical DMARD including methotrexate. Biologics are specifically designed to play an inhibitory role in the inflammatory cascade, either by blocking pro-inflammatory cytokines or by inhibiting or depleting lymphocytes. In most cases, the biologic drug is recommended to be used in combination with a synthetic DMARD. Each biologic has been shown to be effective in suppressing disease activity and joint damage progression in similar percentages of, but not necessarily the same, patients.[22] Despite the fact that in comparative drug trials, combination therapy with a biologic is more effective than methotrexate monotherapy,[23,24] in daily practice most patients do not start with such a combination. Although this strategy is risking insufficient initial response in many of these patients, it is often argued that it is unclear whether this negatively affects long term outcomes. The high costs of biologics are a negative incentive for their early use. The possibility of permanent discontinuation following a rapid clinical improvement might make this argument less valid.

TARGETED TREATMENT

Following early treatment initiation and the option to use biologics, the third factor in the improvement in outcomes for RA patients has been the introduction of targeted treatment. Composite indices of disease activity can be used to set a target at which treatment can be aimed, triggering adjustments as long as the target is not reached. This concept of targeted treatment is closely related to the notion of tight control, which is the practice to measure disease activity at regular intervals of weeks or months, making sure that the target is still met, or adjusting the treatment so that it will be met the next time. Various composite scores of disease activity, including results of clinical assessment as well as laboratory tests and patients opinion, have been developed, initially to be able to compare clinical outcomes between treatment arms of clinical trials.[25-27] Treating to target was first proven to be more effective than interview based treatment decisions in the TICORA trial.[28] In this trial, the disease activity score (DAS) was used to evaluate disease activity and treatment was aimed at low disease activity. Although disease activity scores were designed to evaluate treatment in clinical trials, they proved also to be effective to steer treatment decisions in daily practice.[29]

DISEASE ACTIVITY - OUTCOME MEASURES

Disease activity score

The DAS is a composite index measuring disease activity. It includes a 53 tender joint count (the Ritchie articular index, RAI), a 44 swollen joint count (SJC), erythrocyte sedimentation rate (ESR) and patient's assessment of global health on a 10 cm visual analogue scale (patient's global VAS) , with higher scores indicating worse global health.[27] It can be calculated using the following formula:

$$DAS=0.54\sqrt{RAI} + 0.065(SJC) + 0.33 \ln ESR + 0.072 GH.$$

Patients with a DAS higher than 2.4 are considered to have high disease activity.[30] High disease activity as measured by the DAS is associated with radiological joint damage progression and, more important from a patient point of view: functional disability and decreased health related quality of life.[2,31] It has been suggested that the goal of treatment should be even more stringent: remission.[32] Remission can be defined as a DAS<1.6.[33] An ACR/European League Against Rheumatism (EULAR) task force has suggested an alternative definition, based on tender joint count, swollen joint count (each out of 28 joints, so excluding the feet), C-reactive protein (in mg/dl) and patient's global VAS, where each variable can take a maximum value of 1.[34] Both definitions have similar associations with functional ability and joint damage progression.[35]

Functional ability

Functional ability is considered one of the most important patient reported outcomes in clinical trials.[32] The health assessment questionnaire (HAQ) was designed to measure functional ability in RA patients.[36] It consists of 8 categories which represent dressing, rising, eating, walking, hygiene, reach, grip and errands and chores. Each category has three questions, which can be graded from 0 (no disability) to 3 (unable to do). The highest score in each category is added up and this sum is divided by 8 to get one summary HAQ-disability score. A cut-off of 1 is often used to indicate functional disability.[37,38] A difference of around 0.2 is considered clinically significant.[39] Functional disability in early stages of rheumatoid arthritis is highly correlated with disease activity, indicating that pain and swelling are the most important contributors to functional disability. In older cohorts, in later stages of the disease the correlation with joint damage increases.[40] With effective treatment leading to early suppression of joint damage progression in both small and large joints, functional disability might be delayed or even prevented.

Health related quality of life

A second patient-reported outcome of treatment of rheumatoid arthritis is health related quality of life (HRQoL). This can be measured using the Medical Outcomes Study Short Form 36 (SF-36).[41] This self-administered questionnaire covers 8 areas of health

status: 1) limitations in physical activities because of health problems; 2) limitations in social activities because of physical or emotional problems; 3) limitations in usual role activities because of physical health problems; 4) bodily pain; 5) general mental health (psychological distress and well-being); 6) limitations in usual role activities because of emotional problems; 7) vitality (energy and fatigue); and 8) general health perceptions. The SF-36 scores range from 0 (worst) to 100 (best). Two summary component scores can be derived from the SF-36: one for physical health (PCS) and one for mental health (MCS). These are calculated using norm-based methods that standardize the score to a mean of 50 and an SD of 10 in the general population. In RA, minimum clinically important differences in the PCS and MCS identifying improvements perceptible to patients were defined as a 2.5–5-point change from baseline.[42]

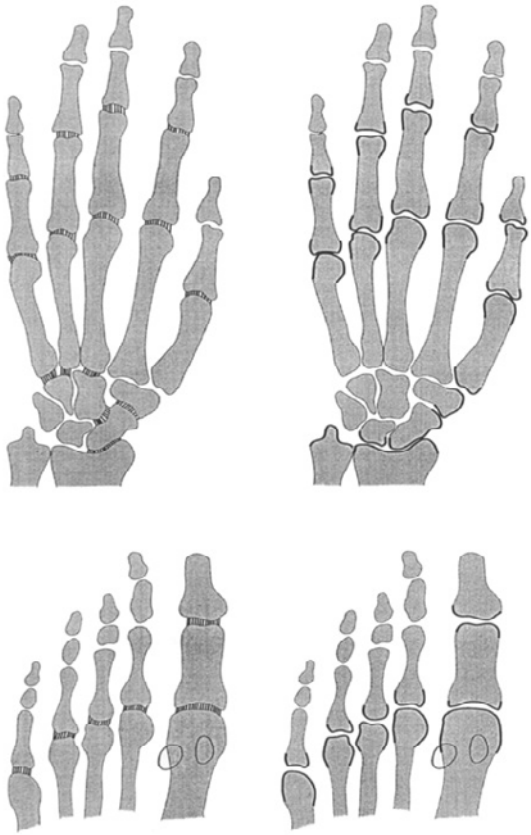

Figure 2: sites of the joints of hands and feet that are scored for joint space narrowing (left panel) and erosions (right panel) using the Sharp-van der Heijde method, adapted from van der Heijde *et al.*[53]

Joint damage

The most common method to evaluate joint damage in trials and in clinical practice is using radiography. For clinical trial purposes, joint damage and damage progression of the hands and feet can be quantified using the Sharp-van der Heijde method.[43] In this method, joint space width and the presence of erosions are evaluated in 44 joints, with a range of 0-4 for joint space narrowing and of 0-5 for erosions, with a maximum total score of 448. To take into account the higher number of evaluated joints in the hands,(*figure 2*) the PIP and MCP joints of the hand can receive a maximum of 5 points for erosions, while the MTP joints can receive a maximum of 10 points. An increase in SHS of at least 5 points has been defined as relevant progression based on expert opinion.[44] An increase of 5 points in the first year of treatment is considered rapid radiological progression (RRP).

To evaluate joint damage in the large joints, the Larsen score for large joints has been developed.[45] Radiographs are scored based on a standard atlas with reference radiographs of the large joints. In the Larsen score, joint space narrowing and erosions are evaluated in one score, ranging from 0 (no abnormality), to 5 (original articular surface has disappeared, gross bone deformation in weight bearing joints). Non-weight bearing joints with erosions receive a score of at least 2, weight bearing joints with erosions a score of at least 3. Damage of the large joints showed a similar correlation with functional disability as damage of the small joints in an older cohort.[2] As large joint damage appears later in the disease than small joint damage, current treatment strategies aiming at quick disease control might result in less large joint damage, and therefore better functional ability.

THE BEST STUDY

The BeSt study was designed to investigate the effect of four different treatment strategies, combined with treatment to target, on clinical and structural outcomes of early rheumatoid arthritis. Between 2000 and 2002, 508 early RA patients (fulfilling the 1987 classification criteria) were included from different hospitals in the west of the Netherlands. They had active disease with at least 6 swollen and 6 painful joints and either a high ESR or a high patient's evaluation of disease activity, and were DMARD naïve. Patients were randomized to four treatment groups: 1. sequential monotherapy, 2. step-up combination therapy, (both starting with methotrexate monotherapy and followed by 3 other synthetic DMARD, in arm 1 consecutively, in arm 2 subsequently added, before patients with persistent insufficient response were eligible for a treatment including the biologic drug infliximab), 3. initial combination therapy with high-dose tapered

prednisolone, or 4. initial combination therapy with infliximab. The treatment effect was evaluated every three months, using the DAS. Joint examination was performed by trained research nurses, blinded for treatment allocation. If low disease activity (DAS≤2.4) was not achieved, treatment was changed or intensified. When low disease activity was achieved for at least 6 months, treatment was tapered to maintenance dose: methotrexate 10 mg/week or sulfasalazine 2000 mg/day (in patients tapering combination therapy with prednisolone). From year three, patients on maintenance dose with a DAS<1.6 for at least 6 months could taper their last DMARD to drug-free. Treatment was restarted when the DAS was ≥1.6 in these patients. Clinical outcomes were evaluated using the HAQ (every three months) and the SF-36 (every three months in the first two years, then yearly). Structural outcomes were evaluated yearly, using radiographs. These were scored in random time order and with concealed patient identity, by two independent readers using the SHS.

Patients who were allocated to the initial combination therapy arms responded earlier to treatment than patients who started with monotherapy. The first evaluation after three months showed 55% and 47% of patients in groups 3 and 4 already achieving the treatment target of DAS ≤2.4 compared to 17% and 19% of patients in groups 1 and 2, respectively.[46] At the end of the first study year, there was no clinically significant difference in functional ability between the 4 treatment groups. After 5 years, there has been no gradual deterioration of functional ability over time, as occurred in earlier RA cohorts. This is probably due to the fact that targeted treatment aiming at DAS ≤2.4 was maintained over the years, and as a consequence, damage progression has been low in the BeSt patients. Annual radiological progression was 1.5, 1.1, 1.5 and 1.6 in years 2-5, but up to the end of the 5th study year, there remained a statistically significant difference in radiological damage progression between groups 1 and 2 on the one hand and groups 3 and 4 on the other. This suggests that initial combination treatment has long-term benefits.[47] For individual patients however, starting with this intensive treatment might not be necessary and the benefits may not outweigh the possible increased risk of adverse events and, in the case of biological therapy, the costs. Therefore, a matrix model that gives a predicted risk of rapid radiological progression (progression ≥5 points SHS in year 1) for each treatment group was developed based on the BeSt data.[48] Predictors for rapid radiological progression are baseline CRP, the presence of rheumatoid factor and/or ACPA and baseline erosion score. With the annual damage progression being so low after year 1, it is unknown whether rapid radiological progression still leads to future disability. Although presence of ACPA was a strong predictor for RRP, after two years of treatment the difference in joint damage progression between ACPA-positive and ACPA-negative patients was only seen in patients initially treated with methotrexate monotherapy.[49] As the difference in suppression of disease activity, which was in favor of

the initial combination therapy groups, disappeared between year 1 and 2 of the study, it is unknown what the role of ACPA is with longer follow-up.
The matrix model showed the lowest risk of RRP in patients using initial combination therapy with infliximab. However there are patients who do not achieve the treatment target on this medication, and being able to predict who will benefit from this medication would be beneficial. It has recently been suggested that high BMI might be associated with poor response.[50] As infliximab is expensive and has the potential downside of infections, the BeSt study included tapering and discontinuation of this drug in those patients who did reach the treatment target for a prolonged period in the protocol. It was shown that tapering and discontinuation is possible, even in patients from groups 1-3, who had failed on previous DMARD, although discontinuation occurred less often in these patients than in the unselected patients in group 4.[51] It is unknown whether long-term discontinuation is possible, and whether we can predict which patients will be able to successfully discontinue. The BeSt study also showed that in patients in prolonged remission, drug-free remission could be achieved.[52] During the first 5 years of the study, 23% of patients at some time achieved drug-free remission. More research into predictors and stop-strategies of both biological therapies and of all medication is needed.
Even though treatment was steered at low disease activity, 48% of patients were in clinical remission at year 5. It is known that lower disease activity corresponds to better functional ability and health related quality of life, but is it unknown whether striving for achieving remission would result in better patient reported outcomes than for low disease activity.

OUTLINE OF THIS THESIS

The current treatment strategies and use of (initial) combination therapy have resulted in significantly improved short-term outcomes for rheumatoid arthritis patients. As the suppression of disease activity and joint damage progression in the BeSt study was maintained during longer follow-up, functional ability could remain stable over time, in contrast to the findings in patients not treated to target.
As besides active disease and small joint damage, the third important contributor to functional ability is large joint damage, in chapter 2 we looked at this association, and at whether early local signs of synovitis can predict local damage in the large joints. In chapter 3 we asked whether large joint damage and small joint damage are associated, and whether large joint damage is, like small joint damage, influenced by treatment strategy. Chapter 4 looks at whether there is an association between rapid radiological progression and future functional ability and joint damage, as yearly damage progression after the first treatment year was so low that it is unknown whether RRP is still

a relevant outcome. As ACPA-positive and ACPA-negative RA might be two different disease entities and in older cohorts ACPA-positivity was associated with decreased treatment response, in chapter 5 we examined the possible difference in functional ability, (drug-free) remission percentages and joint damage progression between ACPA-positive and negative patients. In chapter 6 we asked whether besides being a risk factor for decreased response to TNF-blocker infliximab, high BMI might also be associated with decreased response to other therapies. With the majority of patients showing a good response to infliximab, we looked at the possibility and possible predictors of discontinuation of this costly medication associated with an increased risk for infections after achieving the treatment goal in chapter 7. In chapter 8 we evaluated the current studies examining the possibility and possible predictors of discontinuation of biological agents in general, and in chapter 9 we focused on these questions with regard to achieving drug-free remission. As the current treatment goal is advocated to be either low disease activity or remission, we asked whether achieving remission is associated with better health related quality of life than being in low disease activity in chapter 10.

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Chapter 2

Early local swelling and tenderness are associated with large joint damage after 8 years of treatment to target in patients with recent onset rheumatoid arthritis

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ABSTRACT

Objective To assess whether early swelling and tenderness in large joints in patients with rheumatoid arthritis is predictive of later local damage and whether this leads to functional disability.

Methods Two-year clinical and 8-year radiological follow-up data from the BeSt study, a randomized controlled treat to target trial were used. The association between early local joint swelling and/or tenderness (at least once, or for ≥2 consecutive visits) and later large joint damage (Larsen score ≥1) was assessed using generalized estimating equations. The association between large joint damage and functional ability (HAQ) was assessed using logistic and linear regression analysis.

Results Clinical and 8-year radiological data were available in 290 patients. Concomitant local joint swelling and tenderness at least once in the first 2 years was independently associated with joint damage of the large joints, with an OR of 2.5 (95% CI 1.7;3.6), as was swelling without tenderness: OR 2.0 (95% CI 1.1;3.6). Stronger effects were seen for persistent swelling and/or tenderness. Other independent predictors for joint damage were baseline ESR (OR 1.01 (95% CI 1.01;1.02)) and the presence of RF and/or ACPA (OR 2.5 (95% CI 1.5;4.1) and 2.2 (95% CI 1.3;3.8), respectively). Patients with large joint damage had a higher HAQ after 8 years than patients without (difference 0.15).

Conclusion Early local swelling and tenderness are independent predictors of later joint damage in these joints after 8 years of DAS-targeted treatment in patients with RA. This suggests that suppression of local inflammation could help prevent local damage and functional disability.

INTRODUCTION

Swelling and tenderness in the small joints are associated with radiological damage in these joints in RA patients.[1, 2] Clinical synovitis of the large joints, especially the knees, has also been shown to be predictive of small joint damage, possibly because the presence of a large area of inflamed synovium is correlated with higher systemic levels of pro-inflammatory cytokines.[3] One would assume that large joint inflammation results in local joint damage, but to our knowledge this has never been investigated. In older cohorts, large joint damage is associated with worse functional ability.[4, 5] It is unclear whether this association is still present in patients optimally treated with treatment to target. This we investigated in a large cohort of patients with systematic joint evaluations during 8 years of targeted treatment aiming at low disease activity.

METHODS

Patients

Data from patients from the BeSt study who had radiographs after 8 years of follow-up of ≥2 different large joints were used. The BeSt study is a multi-center randomized controlled trial, in which 508 patients with recent onset RA according to the 1987 American College of Rheumatology criteria were included. All patients gave their written informed consent and the study was approved by the local medical ethics committees of all participating centers. Patients were treated according to a dynamic protocol starting with initial methotrexate monotherapy (sequential or stepwise), combination therapy with prednisolone or combination therapy with infliximab, with treatment adjustments based on assessments of the disease activity score (DAS) performed every 3 months. Treatment was intensified or changed in case of insufficient response (DAS >2.4). If the DAS was ≤2.4 for ≥6 months, medication was tapered to maintenance dose. Starting 2 years after inclusion, patients on monotherapy maintenance dose with a DAS <1.6 for ≥6 months were allowed to taper and stop their last disease modifying anti-rheumatic drug (DMARD). A more detailed description of the study protocol has been published previously.[6]

Study endpoints

Tenderness in the shoulders, elbows, wrists, hips, knees and ankles was assessed every three months by trained research nurses, blinded for treatment allocation, using the Ritchie Articular Index (RAI). It was recoded for the purpose of these analyses as absence of tenderness (RAI 0), or presence (RAI 1, 2 or 3). With the exception of the hips, joints were also scored for swelling (absent or present). Clinical data from the first 2 years after

starting treatment was chosen because disease activity was highest in these years while radiological damage in the small joints was still relatively low. Thus it is unlikely that symptoms in the large joints were due to radiological damage but we have no baseline radiographs of the large joints to confirm this. Mostly due to logistic limitations, only of 290 patients out of 347 patients still in follow-up after 8 years radiographs of the large joints were made. Missing data of at least one joint were found in 76 patients, either because no radiographs were available or because they had prosthesis and no information about the reason for the prosthesis was present. The distribution of missing joints has been published previously.[7] At baseline, patients still in follow-up who did not have large joint radiographs were statistically significantly older (56 vs 52 years), but they had slightly better functional ability (mean HAQ 1.1 vs 1.3). Other baseline characteristics were not statistically different (data not shown). Joint damage in the shoulders, elbows, wrists, hips, knees and ankles consistent with effects of rheumatoid inflammation or secondary arthritis was scored by an experienced musculoskeletal radiologist (HK) using the Larsen score for large joints,[8] ranging from 0 (no damage) to 5 (total destruction). Ten percent of all joints were rescored to assess reliability, with the same score in 93%. A total Larsen score of all 12 joints (maximum 60) was calculated for all patients who had a maximum of 2 missing joint scores. Functional ability was assessed using the Health Assessment Questionnaire. Disability was defined as a HAQ ≥1.9.

Statistical analysis

The relation between symptoms of local inflammation in the first 2 years of treatment and any local joint damage after 8 years (defined as a Larsen score of ≥1, to include minimal damage into the analysis) was evaluated for 'ever signs of inflammation' and next for 'persistent signs of inflammation' by calculating attributable risks. Attributable risks indicate the fraction of added risk in the presence of a certain risk factor, but do not imply causality. Next, we calculated odds ratios (ORs) using generalized estimating equations with an exchangeable covariance structure. This type of analysis takes into account the correlation between different joints within the same patient. The presence or absence of swelling and tenderness was categorized into 4 categories: no swelling or tenderness, tenderness but not swelling, swelling but no tenderness and swelling and tenderness. As swelling could not be determined in the hips, these were not included in the analyses. The models were adjusted for baseline age, erythrocyte sedimentation rate (ESR), body mass index (BMI), gender, treatment strategy, rheumatoid factor (RF) or anti-citrullinated protein antibodies (ACPA) or a combination of these variables and time-averaged DAS of year 0-2. The correlations between HAQ and total Larsen score and between HAQ and DAS after 8 years of treatment were assessed using the Spearman's rank correlation test. Then, the association between having damage in any large joint (total Larsen score ≥1) and the HAQ score was explored using a linear regression

analysis. Subsequently we used logistic regression analysis to investigate if patients with a total Larsen score in the highest tertile had a greater risk of a HAQ score ≥1 compared to patients with a total Larsen score in the lowest tertile. Both estimates were adjusted for DAS at year 8, baseline age, ESR, BMI, gender, treatment strategy, the presence of RF or ACPA, or a combination of these variables.

DAS over 8 years was compared for patients with and without any large joint damage using linear mixed models with a Toeplitz covariance structure, adjusted for baseline age, DAS, BMI, gender, treatment strategy, the presence of RF or ACPA, or a combination of these variables. This analysis was repeated to compare systemic inflammation over 8 years for these patients, with ESR as outcome, adjusted for the same variables, but with baseline ESR instead of baseline DAS.

RESULTS

Radiographs of the large joints were available in 290 patients, 84% of all patients still under follow-up in the BeSt study.(baseline characteristics in *table 1*) Patients with radiological data still in follow-up were younger than the 218 patients no longer in follow-up or without radiographs (mean age at baseline 52 versus 58, p<0.001) and more often treated with combination therapy with infliximab (30 versus 19%) when compared to combination therapy with prednisolone (24 versus 29%, p=0.01) and step-up monotherapy (21 versus 28%, p=0.003). They had a baseline DAS of 4.3 compared to

Table 1: baseline characteristics for all patients with radiological data of at least 2 different large joints after 8 years of treatment (n=290)

Male gender, %	33
Age, mean (SD)	52 (12)
Initial treatment, %	
Sequential monotherapy	25
Step-up monotherapy	21
Combination with prednisolone	24
Combination with infliximab	30
ACPA+ or RF+, %	24
ACPA+ and RF+, %	51
Smoking, %	33
BMI, mean (SD)	26 (4)
DAS, mean (SD)	4.3 (0.9)
HAQ, mean (SD)	1.3 (0.6)
SHS, median (IQR)	2.0 (0.0-5.6)

ACPA anti-citrullinated protein antibodies, *RF* rheumatoid factor, *BMI* body mass index, *DAS* disease activity score, *HAQ* health assessment questionnaire *SHS* Sharp-van der Heijde score

4.5 (p=0.02) and a baseline HAQ of 1.3 compared to 1.5 (p=0.01) in the group of patients without data.

A Larsen score ≥1 was observed in 64/532 (12%) shoulders, 51/538 (10%) elbows, 146/563 (26%) wrists, 67/521 (13%) hips, 95/528 (18%) knees and 39/544 (7%) ankles. A Larsen score ≥1 in at least 1 joint was found in 64% of 290 patients, a Larsen score of ≥2 in at least 1 joint in 37%. Tenderness at least once was observed in 60% of all large joints, at least twice consecutively in 27%. Swelling was observed at least once in 46% and at least twice consecutively in 15%. Patients with radiological damage of large joints (Larsen score ≥1 in at least one large joint) were older at baseline than patients without (54 years old compared to 48, p<0.001) and they had more small joint damage, with a median Sharp-van der Heijde score (SHS) of 3.0, compared to 0.8 (p<0.001).

Swelling and tenderness

Swelling, either in the presence or absence of tenderness showed an association with any local joint damage after 8 years, with ORs of 2.5 (95% CI 1.7;3.6) and 2.0 (95% CI 1.1;3.6) respectively.(*table 3*) The association between tenderness without swelling and any local damage was less strong: OR 1.4 (95% CI 0.97;2.1). These associations were independent of baseline age, ESR, BMI, gender, treatment strategy, rheumatoid factor (RF) or anti-citrullinated protein antibodies (ACPA) or both and time-averaged DAS of year 0-2. Persistent swelling and/or persistent tenderness (present during at least 2 consecutive visits) in the first two years showed an even stronger association with any local joint damage after 8 years. Other independent predictors of large joint damage after 8 years in this model were higher baseline ESR (OR 1.01, 95% CI 1.01;1.02) and the presence of RF or ACPA (OR 2.2, 95% CI 1.3;3.8), or both (OR 2.5, 95% CI 1.5;4.1).

Table 3: the association between local swelling, tenderness or swelling and tenderness with joint damage in shoulders, elbows, wrists, knees and ankles, presented in numbers, as attributable risks per 100 joints and odds ratio's (95% CI)

	At least once			Twice consecutive		
	No with damage/ no at risk (%)	AR (%)	Odds ratio adjusted (95% CI)	No with damage/ no at risk (%)	AR (%)	Odds ratio adjusted (95% CI)
No Swelling or tenderness	70/770 (9.1)	*ref*	*ref*	190/1793 (10.6)	*ref*	*ref*
Tenderness, no swelling	74/703 (10.5)	1.4	1.4 (0.97;2.1)	74/509 (14.5)	3.9	1.6 (1.2;2.2)
Swelling, no tenderness	23/133 (17.3)	8.2	2.0 (1.1;3.6)	31/88 (35.2)	24.6	3.8 (2.2;6.6)
Swelling and tenderness	228/1099 (20.7)	11.6	2.5 (1.7;3.6)	100/315 (31.7)	21.1	3.2 (2.2;4.8)

AR attributable risk *ref* reference category

Table 2: number of joints with swelling and/or pain at least once in years 0-2 per joint

	Elbow		Ankle		Knee		Wrist		Shoulder	
	R	L	R	L	R	L	R	L	R	L
No swelling or pain	130	128	75	62	101	88	44	39	94	66
Pain no swelling	56	75	61	59	63	60	38	44	140	156
Swelling no pain	20	16	13	17	15	22	10	12	5	5
Pain and swelling	84	71	141	152	111	120	198	195	51	63

R right, *L* left

The attributable risk of tenderness was small, but for swelling (with or without tenderness) it varied from 8 to 25 per 100 joints, depending on the duration of swelling.(*table 3*) When stratified for autoantibody status, the attributable risk of having tenderness and swelling was 17 per 100 joints in ACPA and RF positive patients compared to 3 in ACPA and RF negative patients if it was observed at least once, and 26 per 100 joints versus 4 in ACPA and RF negative patients if swelling and tenderness were observed twice consecutively.(*table 4*)

Functional ability and disease activity

The median total Larsen score, which could be calculated for 262/290 patients, was 1 (IQR 0-4). Total Larsen score showed a weak, but significant correlation (Rs 0.2, p=0.001) with the HAQ score at year 8. In comparison, small joint damage (total Sharp-van der Heijde score) at year 8 did not show a correlation with the HAQ score in these patients. The DAS showed a correlation with the HAQ score at year 8 of 0.5 (p <0.001). The difference in HAQ score after 8 years between patients with and without joint damage in ≥1 joint was not clinically relevant: 0.15 (95% CI 0.02;0.28). Patients with a higher total Larsen score (highest tertile, Larsen score ≥4) had a higher risk of functional impairment

Table 4: baseline and attributable risk per 100 joints of (persistent) swelling and tenderness stratified for autoantibody status

	At least once		Twice consecutive	
	Baseline risk (%)	Swelling and tenderness AR (%)	Baseline risk (%)	Swelling and tenderness AR (%)
ACPA and RF -	7/138 5.1	2.7	23/394 5.8	3.7
ACPA or RF +	18/199 9.0	12.4	43/446 9.6	26.6
ACPA and RF +	43/418 10.3	16.6	120/923 13.0	26.3

AR attributable risk, *ACPA* anti-citrullinated protein antibodies, *RF* rheumatoid factor

Table 5: the association between total Larsen score (in tertiles) and disability (HAQ ≥1)

	Odds ratio (95% CI)
Larsen 0	*ref*
Larsen 1-3	1.4 (0.6;3.3)
Larsen ≥4	2.5 (1.01;6.1)

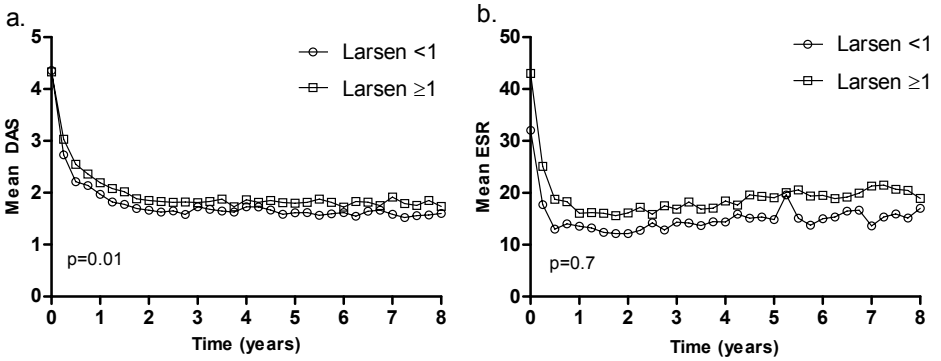

Figure 1: Mean DAS (a) and ESR (b) over time for patients with and without any large joint damage

(HAQ ≥1) compared to patients in the lowest tertile (Larsen score of 0), with an odds ratio of 2.5 (95% CI 1.01;6.1).(*table 5*)

Over 8 years of DAS-targeted treatment, there was a small difference in disease activity between patients with and without damage in any large joint of 0.19 (95% CI 0.05;0.3). (figure 1a) ESR over 8 years was not significantly different for patients with and without damage in any large joint.(*figure 1b*)

DISCUSSION

Swelling, persistent swelling and persistent tenderness in individual large joints during the first 2 years of treatment in patients with recent onset RA were independently associated with joint damage after 8 years in the same joints. Although there was little radiological damage in the large joints, large joint damage showed a statistically significant association with functional ability, whereas small joint damage did not.

The association that was found between clinical signs of synovitis and joint damage in large joints is in line with what was found for damage in small joints.[1, 2] Local suppression of inflammation may also result in local prevention of damage. This was suggested by the finding that less erosions on MRI occurred in metacarpophalangial joints that were treated with intra-articular corticosteroids on top of systemic treatment.[10] Other independent predictors of later large joint damage were higher baseline ESR as indi-

cation of systemic inflammatory activity, and presence of auto-antibodies ACPA and rheumatoid factor, previously also associated with damage progression in general.[11,12] If local treatment of swelling and tenderness could prevent later joint damage, this would be especially beneficial in high risk patients. This is illustrated by the fact that the attributable risk of having swelling and pain at least once is only 3 per 100 joints in ACPA and RF negative patients compared to 17 per 100 joints in ACPA and RF positive patients. This means that if the effects of swelling and tenderness on joint damage could be prevented, this would result in a risk reduction of 17% in autoantibody positive patients compared to 3% in autoantibody negative patients.

In two older cohorts[4,5] a high correlation between large joint damage and functional ability was found. Although, possibly due to DAS-targeted treatment, there was less severe damage in the patients who did show damage (median Larsen score 1) than in older cohorts (median Larsen score 3 in the Drossaers-Bakker cohort), we found a statistically significant correlation between large joint damage and functional ability. Probably related to our finding that damage per joint was less severe than in the older cohorts, the difference in HAQ between patients with or without large joint damage was not above the clinically significant level of 0.19-0.24.[13] As suggested by the analyses by tertile, this difference would most likely be bigger when a more stringent cut-off of large joint damage is used. The difference we found was largely attributable to damage of the wrists (data not shown), as most daily activities inventoried in the HAQ require use of the wrists. In small joints, the association between joint damage and functional ability increases in time,[14] so maybe this 8-year evaluation comes too soon to detect disabling joint damage.

Because in this study baseline radiographs of the large joints or radiographs after 2 years are not available, we cannot determine when joint damage occurred. In theory, tenderness or swelling recorded in the first 2 years of the study might have been the result of early large joint damage. However, since large joint damage usually occurs later in the disease course and is usually preceded by small joint damage,[14-16] which was limited at baseline in our study, swelling and tenderness in the first 2 years after diagnosis are most likely to be the result of local synovitis, and not of joint damage. Of all large joints, 18% was damaged after 8 years without showing any signs of clinical synovitis in the first 2 years of treatment. This may indicate that such damage was the result of inflammation that occurred later in the disease stage, or perhaps of inflammation with subclinical synovitis.[10] We cannot confirm this as there were no other imaging techniques as part of the study protocol. Our experienced musculoskeletal radiologist differentiated between signs consistent with secondary osteoarthritis and signs consistent with primary OA, but it is not impossible that there are joints in the database that received a score of 1 due to primary OA signs. There was a small but statistically significant difference in disease

activity over 8 years follow-up between patients with and without any large joint damage. However, this was not found for systemic inflammation as represented by the ESR. Another potential limitation is that these data from the BeSt cohort are based on a selection of patients who had radiographs available and remained under follow-up. There was no significant difference in large joint swelling and tenderness over 8 years between patients who remained in follow-up with or without radiographs. This indicates that we have no evidence of selection bias, which might influence the association between early large joint swelling and tenderness and later large joint damage. Compared to patients who remained in follow-up, patients no longer in follow-up in the BeSt study were on average older and had slightly higher disease activity at baseline. It is likely that these patients would have had worse functional ability but also possible that they have more large joint damage at year 8 than the patients still under follow-up. This would not affect the association between large joint damage and functional ability that we found.

In conclusion: in this treat to target cohort, early local signs of inflammation are independently associated with local damage in the same large joints after 8 years, although disease activity over 8 years was similar for both patients with and without large joint damage. More than small joint damage, large joint damage is associated with functional disability. This suggests that better suppression of local inflammation could prevent future damage and disability, which would be especially relevant in autoantibody positive patients, as they have an increased risk of large joint damage. Additional studies to determine the long term effects of local treatment are needed to give more insight into whether this can indeed prevent large joint damage and disability.

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Chapter 3

Large joint damage in patients with early rheumatoid arthritis and its association with treatment strategy and damage of the small joints

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ABSTRACT

Objective To determine the prevalence of large joint damage and the association with small joint damage in patients with rheumatoid arthritis (RA) after eight years of low disease activity score (DAS≤2.4)-targeted treatment.

Methods Radiological data of 290 patients participating in the BeSt study, a randomized trial comparing initial monotherapy and initial combination therapy strategies, were used. Radiographs of large joints were scored using the Larsen score, of the small joints using the Sharp-van der Heijde (SHS) score. With multivariable logistic regression analysis an association between total damage of the small joints and of the large joints was investigated.

Results After 8 years of treatment, damage was observed in 12% of shoulders, 10% of elbows, 26% of wrists, 13% of hips, 18% of knees and 7% of the ankles. Damage in ≥1 large joint was found in 64% of patients, with a median score of 1. No difference was found between initial monotherapy or combination therapy strategies. There was a significant association between damage progression in small joints and damage of ≥1 large joint (OR 1.02, 95% CI 1.00;1.04).

Conclusion After 8 years of DAS-targeted treatment in early RA patients, large joint damage was found in 64% of patients and was associated with small joint damage. Continued DAS-targeted treatment is more important in damage suppression than initial treatment strategy. Patients with more damage of hands and feet also have more damage of the large joints.

INTRODUCTION

Radiographic damage in the small joints (hands and/or feet) occurs in most patients with rheumatoid arthritis (RA) in the early years of disease.[1-3] Damage of the large joints (shoulders, elbows, hips, knees and ankles) usually has a later onset.[4,5] Since damage of the large joints has an even larger impact on functional ability than small joint damage[6,7] prevention of large joint damage is a relevant goal in RA treatment. However, large joints are not routinely monitored for damage progression in RA.

In older cohorts, damage progression in small and large joints was highly correlated.[6,7] It is not known if this is still the case, now that disease activity targeted treatment strategies and new (combinations of) anti-rheumatic drugs have shown to adequately suppress damage progression in small joints in many patients.[8-10]

Therefore, we looked at the prevalence of radiological damage in large joints in a disease activity score (DAS)-targeted treatment cohort of RA patients with 8 years of disease duration and investigated whether there is still a relation with damage progression in small joints, and we investigated whether such a relation depends on small joints erosiveness or joint space narrowing and whether it was influenced by the initial therapy.

METHODS

Patients

All data were collected in the BeSt study, a randomized clinical trial comparing four different treatment strategies in patients with recent onset RA (revised 1987 American College of Rheumatology (ACR) criteria). Patients were randomized to one of four treatment strategies: (1) sequential monotherapy, (2) step-up therapy, (3) initial combination therapy with tapered high-dose prednisolone or (4) initial combination therapy including infliximab. Every three months, treatment adjustments were made based on the DAS and treatment aimed at a DAS ≤2.4. More details on the BeSt study design were previously published.[11,12] At year 8, radiographs of the large joints were made for 290/347 patients who were still under follow-up. In 57/347 of the patients radiographs were not made, mostly due to logistic reasons in the different hospitals, but also because a small number of patients refused.

Assessment of radiological damage

Radiographs of the shoulders, elbows, wrists, hips, knees and ankles were scored by an experienced musculoskeletal radiologist (HK) using the Larsen score (range 0-5 per joint).[13] Only joints showing specific signs of damage caused by rheumatoid arthritis inflammation or secondary osteoarthritis, not primary osteoarthritis, according to HK

were scored as having damage. Intra-reader reliability was determined based on a rescore of a random 10% of all radiographs, separately for each joint, with intraclass correlation coefficients of 0.78 for the shoulders, 0.98 for the elbows, 0.89 for the wrists, 0.96 for the hips, 0.98 for the knees and 0.65 for the ankles. Overall, 93% of all rescored radiographs were given the same score twice. Large joint damage was defined as a total Larsen score ≥1 (at least one joint with damage ≥1 point). For the total Larsen score, all separate joint scores of patients who had no more than 2 joint scores missing were added up (maximum 60). Radiographs of the hands and feet were taken at baseline and yearly up to year 8 and scored according to the Sharp-van der Heijde Score (SHS). Two independent readers (LD and MB) scored these radiographs blinded for time order and patient identity and the mean progression score of the two readers was used for the analysis. The inter-observer intraclass correlation coefficient (ICC) was 0.96. Two thresholds of radiological damage progression of the small joints of hands and feet were defined: an increase in SHS scores ≥5 points (based on the smallest detectable change) or an increase of ≥15 points (the highest 20%) over eight years time.

Statistical analysis

Demographic and clinical baseline characteristics for patients with and without damage ≥1 point total Larsen were compared. Differences were tested using the chi-square test for categorical data and either the Student's T-test or Mann Whitney U test for continuous data, depending on the distribution of the tested variable. The distribution of damage in the individual large joints was analyzed with a cluster analysis (TreeView, version 16) in order to identify whether specific patterns of joint involvement occur.

Subsequently, a multivariable logistic regression analysis was performed to identify an association between damage in the large joints and radiological damage progression in the small joints over eight years time. For these analyses the wrists were not included in the large joint score but only in the SHS. In the analysis small joint damage was entered first as a continuous variable and next as a dichotomous variable with cut-offs of ≥5 points SHS and ≥15 points SHS. Estimates were adjusted for gender, treatment strategy, rheumatoid factor (RF), anti-citrullinated protein antibodies (ACPA) or a combination of RF and ACPA, and baseline age, erythrocyte sedimentation rate (ESR) and SHS. In addition, multivariable logistic analyses were repeated for narrowing and erosions separately and simultaneously to determine if narrowing or erosion scores were independently associated with damage in the large joints. Estimates were adjusted for gender, treatment strategy, RF, ACPA or a combination of RF and ACPA, and baseline age, ESR and narrowing and/or erosion score. To analyze the data, SPSS version 17.0 software (SPSS, Chicago, IL, USA) was used. All tests were two-tailed and $p<0.05$ was considered to be statistically significant.

RESULTS

Patient characteristics, separately for patients with and without damage of the large joints, are shown in table 1. Patients were on average 52 years old, most were female (67%), had an average BMI of 26 and 67% and 60% of the patients were RF and ACPA-positive, respectively. At baseline, disease was active with a mean DAS of 4.3, mean ESR of 41 mm/hr, ant the mean HAQ was 1.3. In 40% of the patients erosive disease of the small joints was present, and the median SHS score at baseline was 2 points.

The 290 patients with large joint radiographs were younger (52 versus 58 years) and had a slightly lower DAS (4.3 versus 4.5) and HAQ (1.3 versus 1.5) and a higher median SHS (2.5 versus 2 points) than the 218 other patients in the BeSt cohort who were no longer under follow-up or did not have large joint radiographs made. Further, more patients with large joint radiographs had been treated with initial combination therapy with infliximab and less with initial combination therapy with prednisolone or with step-up combination therapy.

Table 1: baseline characteristics of 290 out of 508 recent-onset RA patients in the BeSt study

Baseline characteristics	All patients (n=290)	Patients without damage (n=128)	Patients with damage (n=162)	p-value
Age, mean ± SD years	52 (12)	49 (11)	54 (12)	<0.001
Female gender, n (%)	195 (67)	84 (66)	111 (69)	0.60
Symptom duration, median (IQR) weeks	23 (14-52)	23 (13-51)	24 (14-53)	0.76
DAS, mean ± SD	4.3 (0.9)	4.3 (0.9)	4.4 (0.8)	0.69
HAQ, mean ± SD	1.3 (0.6)	1.3 (0.6)	1.4 (0.7)	0.44
BMI, mean ± SD	26 (4)	26 (4)	26 (4)	0.69
ESR, mean ± SD	41 (27)	34 (22)	43 (29)	<0.05
SHS, mean ± SD	4 (6)	3 (6)	5 (6)	<0.05
Total Larsen score, median (IQR)	1 (0-2)	0 (0-0)	2 (1-4)	<0.001
RF positive, n (%)	192 (67)	80 (63)	112 (69)	0.24
ACPA-positive, n (%)	173 (60)	72 (57)	101 (62)	0.31
Smoking yes, n (%)	95 (33)	46 (36)	49 (30)	0.28
Treatment strategy				0.94
Sequential monotherapy	73 (25)	30 (23)	43 (27)	
Step-up therapy	60 (21)	27 (21)	33 (20)	
Initial combination with prednisolone	70 (24)	31 (24)	39 (24)	
Initial combination with infliximab	87 (30)	40 (31)	47 (29)	

DAS disease activity score, *HAQ* health assessment questionnaire, *BMI* body mass index, *ESR* erythrocyte sedimentation rate, *SHS* Sharp-van der Heijde Score, *IQR* inter-quartile range, *RF* rheumatoid factor, *ACPA* anti-citrullinated protein antibodies

Patients were categorized with and without damage ≥1 point of the total Larsen score in the large joints

Radiological damage in the large joints

Joint damage (≥1 point Larsen) was observed in 64/532 (12%) of the shoulders, 51/538 (10%) of the elbows, 146/563 (26%) of the wrists, 67/521 (13%) of the hips, 95/528 (18%) of the knees and 39/544 (7%) of the ankles. Sixty-four percent of the patients had damage in at least 1 large joint. Of the patients with damage, 31% had damage in only one joint, 24% in 2 joints, 13% in three joints and 32% in four or more joints.(*figure 1*) Mean (SD) total Larsen score was 2.7 (3.7) and median (IQR) total Larsen score was 1 (0-4). The cluster analysis identified clusters of bilateral damage in the wrists, the knees, hips and elbows (right wrist clusters with left wrist, right knee with left knee, etc.), showing that symmetrical involvement in RA extends to symmetrical damage of the joints.(*figure 2*)
Seven percent of the patients had one or more joint prostheses; two elbows, two wrists, 15 hips, 14 knees and one ankle prosthesis. Most patients (52%) had one prosthesis, 33% had prostheses in two joints and 14% had prostheses in three joints. In 50% of the cases prostheses were placed because of degenerative joint disease (primary osteoarthritis), in 35% because of secondary osteoarthritis, in 12% due to other reasons such as fracture or dysplasia and in 3% the reason was unknown.
There was no significant difference in median total Larsen scores between patients initially treated with monotherapy and patients initially treated with combination therapy. The median (IQR) total Larsen in the initial monotherapy group was 1.5 (0-5), 2 (0-4) in the step-up group and 1 (0-3) both in the initial combination therapy with prednisolone group and the initial combination therapy with infliximab group.

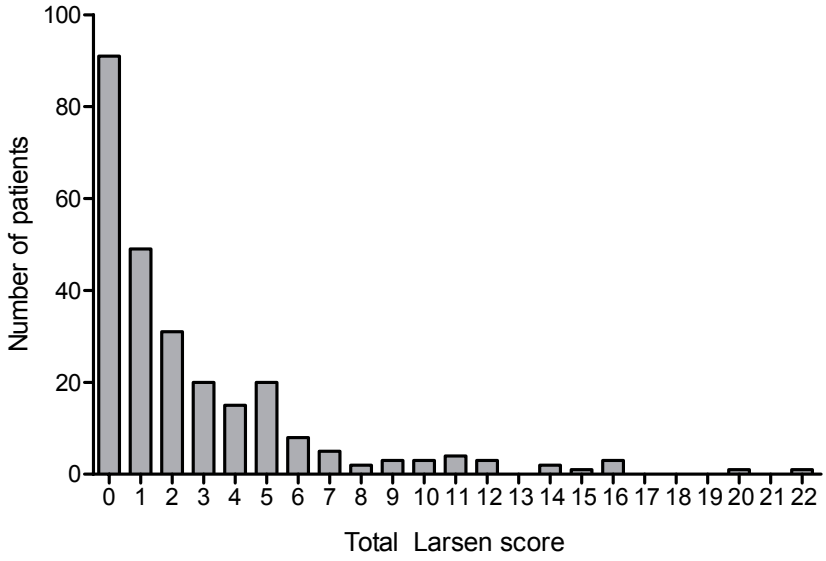

Figure 1: Frequencies of total Larsen scores of 290 patients, after 8 years of treatment

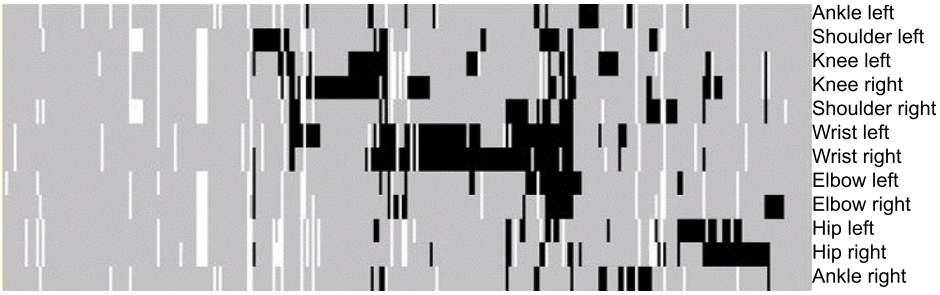

Figure 2: Cluster analysis to identify specific patterns of joint involvement
Each column represents a specific patient and each row a specific joint. Black indicates that a patient has damage (≥1 point Larsen score) in that specific joint, grey indicates no damage and white indicates that a joint score is missing.

Seventy-two percent of the 290 BeSt patients in this analysis had radiological damage (>0.5 point) of the small joints after 8 years. Thirty-three percent of the patients had progression ≥5 points SHS and 19% had progression ≥15 points SHS in 8 years. Mean (± SD) damage progression was highest in the first year (2.7 ± 11) and stabilized thereafter with a mean (SD) progression of 1.2 (4) SHS points per year in these patients. Patients with large joint damage (total Larsen without wrists ≥1) had more small joint damage progression per year than patients without large joint damage,(figure 3) but the difference was only significant in the first year of treatment: mean (SD) SHS progression in patients with large joint damage 4 (13) and in patients without large joint damage 1 (4) ($p<0.05$).

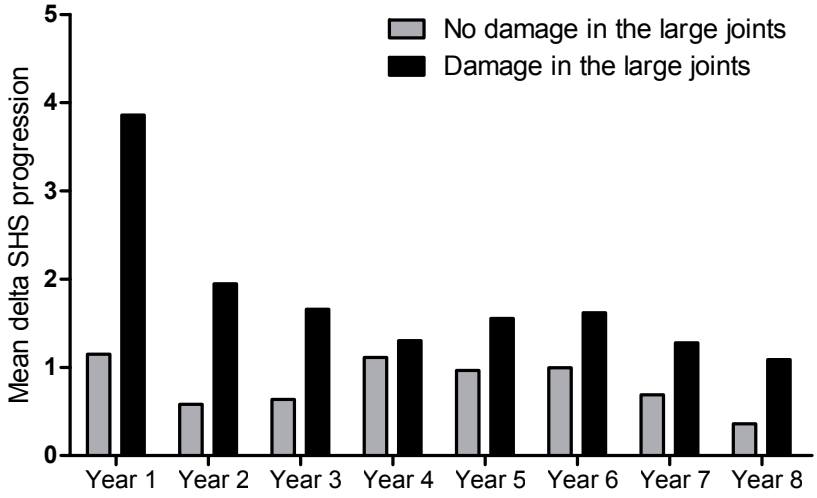

Figure 3: Mean radiological damage progression (SHS) of the small joints per year, separately for patients with and without large joint damage

Table 2: associations between radiological damage progression in the small joints (model 1 with delta SHS, model 2 with ≥5 and model 3 with ≥15 points SHS) and damage ≥1 point in at least one large joint, presented in odds ratios (OR) and their 95% CI

		Crude odds ratio (95% CI)	Adjusted odds ratio* (95% CI)
Model 1	Delta SHS 0-8	1.03 (1.01;1.05)	1.02 (1.00;1.04)
Model 2	<5	*ref*	*ref*
	≥5	2.6 (1.5;4.4)	2.0 (1.1;3.8)
Model 3	<15	*ref*	*ref*
	≥15	3.3 (1.7;6.7)	2.6 (1.2;5.6)

*Adjusted for gender, treatment strategy, RF/ACPA/combination of RF and ACPA, baseline SHS, age and ESR

Radiological damage progression in small joints (SHS) was significantly associated with damage of the large joints with an odds ratio (OR) of 1.02 (95% CI 1.00;1.04). Radiological damage progression ≥5 points and ≥15 points SHS were both independently associated with damage ≥1 total Larsen score in the large joints, with ORs of 2.0 (95% CI 1.1;3.8) and 2.6 (95% CI 1.2;5.6), respectively.(*table 2*) Thus, patients with more damage progression in small joints had a higher risk of damage of the large joints.

Both an increase in joint space narrowing and an increase in erosion score over 8 years were significantly associated with damage of the large joints (OR 1.04, 95% CI 1.00;1.07 and OR 1.05, 95% CI 1.01;1.09, respectively), but when both were entered in one model, neither was independently associated with damage of the large joints (OR 1.03, 95% CI 0.97;1.09 and OR 1.02, 95% CI 0.97;1.07, respectively).

DISCUSSION

After 8 years of treatment, 64% of the patients with RA have developed radiological damage in large joints, despite tight control DAS-targeted therapy adjustments aimed at low DAS (≤2.4). The percentage we found (64%) is similar to what was reported in non-DAS-targeted treated historical cohorts, but the per patient severity was less.[6,7] In patients from our Rheumatoid Arthritis Patients in Training (RAPIT) trial who were matched for 8 years symptom duration, the percentage of patients with large joint damage was 79%.[14] Since patients in the BeSt cohort were selected on active disease at baseline, the observed difference may be the result of earlier and DAS-targeted treatment in our cohort. Similar results were previously found for small joint damage.[7,8] Further, in the RAPIT cohort radiographs of the tarsus and not of the wrists were used for the total Larsen score, while in the BeSt cohort radiographs of the wrists and not the tarsus were used. However, since in the BeSt cohort the wrists were most often and severely damaged, it

is unlikely that we underestimated the total large joint damage in that cohort. Although in the BeSt cohort more patients had been treated with initial combination therapy including prednisolone or infliximab, it is unlikely that this explains the difference in large joint damage between the cohorts, since in a separate analysis in the BeSt cohort we found no difference in large joint damage between patients initially treated with monotherapy (sequential or step-up) and patients initially treated with combination therapy (including either prednisolone or infliximab). This was different in the FIN-RACo study, where after 11 years of treatment there was less large joint damage in the initial DMARD combination therapy group than in the DMARD monotherapy group.[15] In the first 2 years of FIN-RACo, there were less treatment adjustments than in the first years of the BeSt study, resulting in a considerable difference in clinical response still after 1 year of treatment. In the BeSt study there was a statistically significant difference in small joint damage progression between the initial monotherapy groups and the initial combination therapy groups in the first years of treatment, but in the following years this difference is lost due to the larger effect of similar low disease activity in all treatment groups, as a result of continued frequent DAS-targeted treatment adjustments.[11,12] For large joint damage, the effect of initial treatment strategy may be similar to the effect on small joint damage, but since large joint damage tends to occur later in the course of the disease, when disease activity in the BeSt study was well suppressed, the continued DAS-targeted treatment may be even more effective.[4,5]

In contrast to previous studies,[6,7] our cohort was treated according to a DAS-targeted protocol, resulting in significantly better suppression of damage progression in the small joints.[8,11,12,16] Therefore we expected also little damage in the large joints, resulting in a smaller or even absent association between small and large joint damage. However we did find in this DAS-targeted BeSt cohort that total small joint damage progression is associated with large joint damage. Neither small joint erosions nor small joint space narrowing score were independently associated with damage in the large joints. To our knowledge we are the first to examine these features of joint damage separately.

Interpreting radiographic damage in the large joints can be difficult since damage may also be caused by primary degenerative processes or osteoarthritis, which may be found in a substantial number of older patients, or secondary osteoarthritis due to other causes than RA.[17,18] Experienced musculoskeletal radiologists such as HK recognize patterns of damage both within and between large joints as primary degenerative damage or as rheumatoid damage. Nevertheless, we cannot rule out the possibility of an overestimation of large joint damage in our cohort. The fact that patients with large joint damage were on average older may suggest this. Still, including non-rheumatic damage in our analysis would result in an underestimation of the association between small and large joint damage rather than an overestimation. Therefore, we do not think that this possibility undermines our conclusions.

In 7% of the evaluated patients in this cohort joint replacement surgery had occurred, which is a similar prevalence as previously reported.[6, 19] This would suggest that severely damaged joints occurred as often as in older cohorts. Since we have excluded the joints with a replacement from our analysis, one might even argue that we have underestimated large joint damage. However, the medical records showed that the majority of joint replacements were due to osteoarthritis and not rheumatoid arthritis. And it is likely that, in comparison to older cohorts, patients in the BeSt cohort had joint replacement surgery in relatively less damaged joints, due to advanced technical possibilities, shorter waiting lists and changed insights in timing of joint replacements.

In conclusion, after 8 years of DAS-targeted treatment, a similar percentage of patients with some damage, and a similar percentage of joint replacements was found as was reported in historical cohorts. However, per patient large joint damage appeared to be less severe. Possibly reflecting the benefit of 8 years of targeted treatment, no difference in large joint damage between patients initially treated with monotherapy and patients initially treated with combination therapy was found. As in older cohorts, large joint damage was found to be associated with damage in small joints of the hands and feet. This implies that monitoring small joint damage is sufficient to guide treatment decisions in order to prevent large joint damage and long term disability.

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Chapter 4

Rapid radiological progression in the first year of early RA is predictive of disability and joint damage progression during 8 years of follow-up: post hoc analyses from the BeSt study

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ABSTRACT

Objective Several prediction models for rapid radiological progression (RRP) in the first year of RA have been designed to aid rheumatologists in their choice of initial treatment. We assessed the association between rapid radiological progression and disability and joint damage progression in 8 years.

Methods Patients from the BeSt cohort were used. RRP was defined as an increase of ≥5 points Sharp-van der Heijde Score (SHS) in year 1. Functional ability over 8 years, measured with the Health Assessment Questionnaire (HAQ), was compared for patients with and without RRP using linear mixed models. Joint damage progression from year 1-8 was compared using logistic regression analyses.

Results RRP was observed in 102/465 patients. Over 8 years, patients with RRP had worse functional ability: difference in HAQ score 0.21 (0.14 after adjustment for DAS over time). RRP was associated with joint damage progression ≥25 points SHS in year 1- 8: odds ratio 4.6.

Conclusion Rapid radiological progression in year 1 is a predictor of worse functional ability over 8 years, independent of baseline joint damage and disease activity. Patients with RRP have more joint damage progression in subsequent years. This makes RRP a relevant outcome to base the initial treatment decision on.

INTRODUCTION

Minimizing joint damage (progression) to prevent disability is an important treatment goal of rheumatoid arthritis.[1] Several prediction models have been designed to identify patients at risk of rapid radiological progression in the first year of treatment (RRP), in order to individualize initial treatment strategies.[2,3] But is there clinical relevance in whether or not a patient has rapid radiological damage progression? To our knowledge, it has not been investigated whether RRP is associated with functional disability in subsequent years. Therefore we asked whether patients with RRP in year one, defined as an increase in Sharp-van der Heijde Score (SHS) of ≥5,[4] had worse functional ability in the first 8 years of treatment. Secondly we investigated whether RRP is a predictor of subsequent joint damage progression.

METHODS

Patients

All patients with radiological data at baseline and after 1 year of treatment from the BeSt cohort were analyzed (465/508). Patients included in the BeSt study, a randomized controlled trial, were treated according to 4 treatment strategies, aimed at a disease activity score (DAS) ≤2.4. Initial therapy was sequential or step-up monotherapy (starting with methotrexate) or combination therapy with prednisolone or with infliximab. If the DAS was ≤2.4 for ≥6 months, medication was tapered to monotherapy. Details of the BeSt study were published previously.[5]

Study endpoints

To evaluate radiological progression, the Sharp-van der Heijde score was used. Radiographs from baseline and year 1 were scored by two readers, blinded for patient identity and time order. The average progression score of these readers was used to classify patients as with RRP (change in SHS ≥5) or without (change <5). This threshold is similar to the smallest detectable difference (SDD) of the first study year.[5] Radiological progression from year 0-8 was assessed by two other readers according to the same method, using radiographs of years 0-1-2-3-4-5-6-7-8. The inter-observer intraclass correlation coefficient was 0.96. Functional ability and disease activity were measured every 3 months using the Health Assessment Questionnaire (HAQ) and DAS respectively.

Statistical analysis

The HAQ score over 8 years was compared for patients with and without RRP using linear mixed models, to incorporate missing patient data, with a Toeplitz covariance structure.

The estimate was adjusted for treatment group, baseline ESR, HAQ, SHS and the presence of rheumatoid factor (RF), anti-citrullinated protein antibodies (ACPA) or both. To assess the contribution of disease activity to functional ability over time, the analysis was repeated adjusted for these variables and for DAS over time. The mean HAQ over time was calculated using these models and depicted in a graph. Because the definition of RRP was relatively arbitrary, we investigated if patients with even more progression in year 1 would also show more disability. We divided all patients into deciles of SHS change in year 1. The lowest score of the 9th and 10th decile were 5.5 and 9.5 respectively. We used data driven cut-offs to avoid multiple testing. HAQ over time was compared for patients with a progression score of <5.5 or ≥5.5 and for patients with a progression score of <9.5 or ≥9.5, using linear mixed models as described above. To compare disease activity over time for patients with and without RRP, linear mixed models with a Toeplitz covariance structure were used. The analysis was adjusted for treatment group, baseline DAS, SHS and RF, ACPA or RF and ACPA. Adding age and gender to this model or the models with HAQ did not change the results, nor did adding an interaction term between RRP and treatment group.

Joint damage progression from year 1-8 was compared for patients with and without RRP using the Mann-Whitney U test. Logistic regression analyses were then used to compare risk of damage progression of ≥5 (SDD) and ≥25 points (progression in the 10% of patients with highest progression scores in years 1-8), adjusted for treatment group, baseline ESR and SHS and RF/ACPA or RF and ACPA.

RESULTS

RRP was observed in 102/465 (22%) patients. Patients with RRP were more often ACPA and RF positive and treated with initial monotherapy. Patients with RRP had a higher baseline ESR (54 versus 37 mm/hr, p-value <0.001) and CRP (60 versus 31, p-value <0.001). They had worse functional ability (HAQ 1.5, versus 1.4, p-value 0.04) and more radiological damage: median baseline SHS 5.8 versus 1.5, p-value <0.001.(*table 1*) The number of treatment steps patients had failed on and the number of patients failed on all protocol steps after 8 years was higher in patients with RRP, p-values 0.001 and <0.001. At year 8, 133/465 patients were lost to follow-up: 29% of patients without RRP, 27% of patients with RRP, p=0.6. Differences in baseline characteristics for patients without and with radiological progression ≥9.5 in year 1 were comparable to these results.(*table S1*)

Functional ability

Over 8 years, there was a statistically significant difference (0.21 (95% CI 0.10;0.33)) in HAQ score for patients with and without RRP.(*figure 1*) For groups 1 and 2 the difference was 0.20

Table 1: baseline characteristics of patients with and without RRP after 1 year of DAS-targeted treatment

	Without RRP (n=363)	With RRP (n=102)	p-value
Female gender, %	67	72	0.3
Age	54 (13)	55 (13)	0.5
Symptom dur., wks, median (IQR)	24 (14-52)	24 (14-58)	0.5
ACPA pos, %	57	77	<0.001
RF pos, %	60	82	<0.001
Smoker, %	35	36	0.9
Initial treatment, %			<0.001
Sequential monotherapy	20	40	
Step-up monotherapy	21	33	
Combination with pred	29	16	
Combination with ifx	31	11	
BMI	26 (4)	26 (4)	0.9
DAS	4.4 (0.8)	4.5 (0.9)	0.07
ESR	37 (24)	54 (33)	<0.001
CRP	31 (37)	60 (56)	<0.001
HAQ	1.4 (0.7)	1.5 (0.7)	0.04
SHS, median (IQR)	1.5 (0.0-4.0)	5.8 (2.0-11.5)	<0.001
Treatment steps failed on, median (IQR)	1 (1-3)	3 (1-5)	0.001

ACPA anti-citrullinated protein antibodies, *RF* rheumatoid factor, *BMI* body mass index, *DAS* disease activity score, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *HAQ* health assessment questionnaire score, *SHS* Sharp-van der Heijde Score
Data are presented as mean (SD), unless stated otherwise

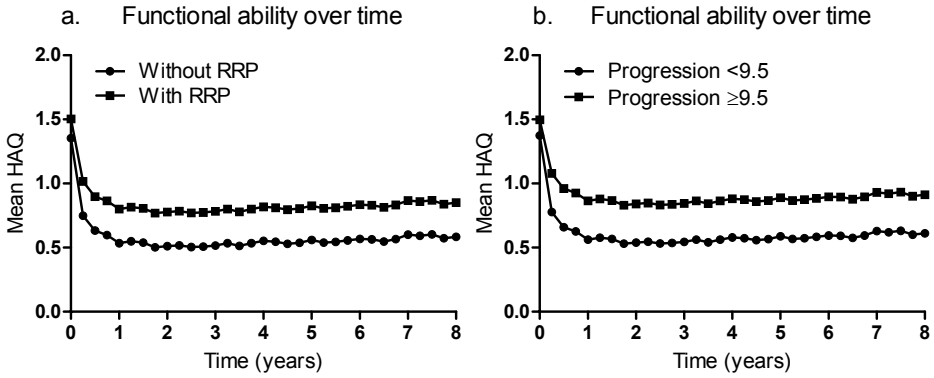

Figure 1: Mean Health Assessment Questionnaire score (HAQ) over 8 years for patients with and without rapid radiological progression SHS ≥5 in year 1 (RRP) (a) and for patients with progression <9.5 or ≥9.5 points in year 1 (b)
Adjusted for baseline HAQ, treatment strategy, baseline ESR and Sharp-van der Heijde Score and presence of RF and/or ACPA (using linear mixed models, which take into account missing patient data)

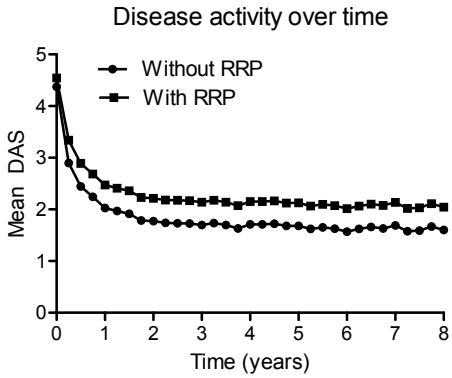

Figure S1: Disease activity over time for patients with and without rapid radiological progression in year 1, mean estimated values from linear mixed models

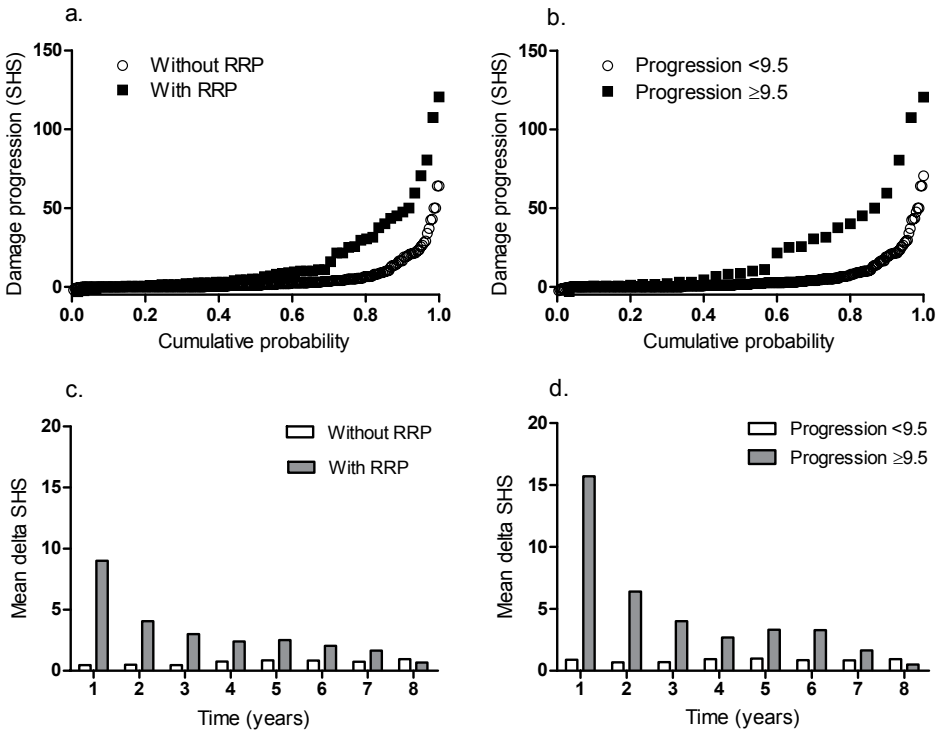

Figure 2: Joint damage progression in year 1-8 and yearly joint damage progression over time for patients with and without rapid radiological progression SHS ≥5 in year 1 (RRP) (a and c), and for patients with <9.5 or ≥9.5 points progression in year 1 (b and d)
n (no RRP/RRP) yr 1: 363/102, yr 2: 326/85, yr 3: 305/81, yr 4: 296/82, yr 5: 272/78, yr 6: 236/64, yr 7: 221/61, yr 8: 216/61

Table S1: a comparison of baseline characteristics for patients with <9.5 and ≥9.5 points (SHS) damage progression in the first year of treatment

	<9.5 points progression (n=421)	≥9.5 points progression (n=44)	p-value
Female gender, %	68	66	0.8
Age, mean (SD)	54 (13)	54 (13)	0.7
Symptom duration, wks, median (IQR)	24 (14-51)	23 (13-71)	0.4
ACPA pos, %	59	84	0.001
RF pos, %	62	86	0.001
Smoker, %	34	46	0.2
Initial treatment, %			<0.001
Sequential monotherapy	22	48	
Step-up monotherapy	24	30	
Combination with pred	27	14	
Combination with ifx	28	9	
BMI, mean (SD)	26 (4)	25 (4)	0.2
DAS, mean (SD)	4.4 (0.9)	4.6 (0.8)	0.1
ESR, mean (SD)	38 (25)	66 (37)	<0.001
CRP, mean (SD)	35 (14)	66 (51)	<0.001
HAQ, mean (SD)	1.4 (0.5)	1.5 (0.7)	0.4
SHS, median (IQR)	2.0 (0.0-6.0)	5.8 (1.3-10.9)	0.003

ACPA anti-citrullinated protein antibodies, *RF* rheumatoid factor, *BMI* body mass index, *DAS* disease activity score, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *HAQ* health assessment questionnaire score, *SHS* Sharp-van der Heijde Score
Data are presented as mean (SD), unless stated otherwise

(95% CI 0.05;0.34), for groups 3 and 4: 0.27 (95% CI 0.08;0.45). DAS over time in RRP patients was also higher than in non-RRP patients: difference 0.33 (95% CI 0.18;0.48).(*figure S1*) After adjustment for DAS over time, the difference in HAQ score was statistically, but not clinically significant: 0.14 (95% CI 0.05;0.24). The difference in HAQ score between the 10% of patients with the highest progression score in year 1 and the other 90% was 0.27 (95% CI 0.12;0.41), 0.20 (95% CI 0.08;0.33) after adjustment for DAS over time. The difference in HAQ score for patients with and without damage progression ≥5.5 (top 20% of progression scores versus the other 80%) was 0.15 (95% CI 0.06;0.25) after adjustment for DAS over time.

Joint damage

Patients with RRP in year 1 had more joint damage progression in year 1-8,(*figure 2*) with a median progression score of 5.0 (IQR 1.5-25.3) compared to 1.0 (IQR 0.0-5.0) for patients without RRP (p<0.001). The OR of ≥5 points progression was 2.0 (95% CI 0.96;4.2). Patients with RRP had an increased risk of damage progression ≥25 in year 1-8: OR of 4.6 (95% CI 1.6;12.7). Of the patients without RRP, 5% had more than 25 units progression in years 1-8. The mean yearly progression score was never higher than the SDD (5) in either group.

When comparing the 10% of patients with the highest progression score in year 1 to the other 90% (cut-off 9.5), similar results were seen for progression ≥5 in year 1-8: OR 1.8 (95% CI 0.7;4.5). The risk of being in the top 10% of progression scores again in years 1-8 (progression ≥25) was higher: OR 6.6 (95% CI 2.2;19.8). The median progression score in year 1 in these patients was 15.5 points SHS (IQR 12.5-22.0).

DISCUSSION

Rapid radiological progression, defined as an increase of ≥5 points in Sharp-van der Heijde score in the first year of treatment, is associated with worse functional ability in later years and more radiological damage progression. This can only be partly explained by higher disease activity in these patients. Our results show that rapid radiological progression is a clinically relevant outcome to be used in prediction models that can help choose the best initial treatment for patients with newly diagnosed RA.

The impact of rapid radiological progression with this threshold on functional ability is relatively small. Based on an estimated minimally important difference (MID) of the HAQ score of 0.20-0.24,[6] the statistically significant difference in HAQ over 8 years explained by RRP, not disease activity, was not clinically relevant. Probably this is because the follow-up period of 8 years is still short. More importantly, after the first 1-2 years yearly damage progression in all patients is much lower and shows a tendency to decrease with time.(*figures 2c and 2d*) This is most likely due to the continuous three-monthly DAS ≤2.4 steered treatment adjustments in the BeSt cohort, resulting in low disease activity in the vast majority of patients. Still, yearly progression in patients with RRP continues to be higher than in patients without RRP, who hardly progress at all. We found that patients with RRP have an increased risk of subsequent joint damage progression. Combined with the effect of ageing,[7] after a longer follow-up period, this continuous damage progression may lead to significantly more functional disability. Our results also show that the 10% of patients who had an increase of ≥9.5 points SHS in the first year have even worse functional ability after 8 years. We found a clinically meaningful difference in mean HAQ score between these 10% and the other patients after adjustment for disease activity over time.

In conclusion, rapid radiological progression in the first year of treatment is an independent predictor of later functional disability and thus not only a radiologically but also a clinically relevant early outcome to base the initial choice of treatment on. This may mean that, as earlier studies have shown[2,3], patients with a low risk of RRP require less intensive initial therapy to prevent radiological damage progression than patients with a high risk, provided that this therapy offers early symptom relief and provided treatment remains 'treat to target'.

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Chapter 5

The association of treatment response and joint damage with ACPA status in recent onset RA: a subanalysis of the 8-year follow-up of the BeSt study

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ABSTRACT

Objective Anti-citrullinated protein antibodies (ACPA) are suggested to identify different subsets of patients with rheumatoid arthritis (RA). The authors compared the clinical and radiological response to Disease Activity Score (DAS)-steered treatment in patients with RA positive or RA negative for ACPA.

Methods In the Behandel Strategieën (BeSt) study, 508 patients with recent onset RA were randomized to four treatment strategies aimed at a DAS ≤2.4. Risks of damage progression and (drug-free) remission in 8 years were compared for ACPA-positive and ACPA-negative patients, using logistic regression analysis. Functional ability and DAS components over time were compared using linear mixed models.

Results DAS reduction was achieved similarly in ACPA-positive and ACPA-negative patients in all treatment strategy groups, with a similar need to adjust treatment because of inadequate response. Functional ability and remission rates were not different for ACPA-positive and ACPA-negative patients. ACPA-positive patients had more radiological damage progression, especially after initial monotherapy. They had a lower chance of achieving (persistent) drug-free remission.

Conclusion Clinical response to treatment was similar in ACPA-positive and ACPA–negative patients. However, more ACPA-positive patients, especially those treated with initial monotherapy, had significant radiological damage progression, indicating that methotrexate monotherapy and DAS ≤2.4 steered treatment might be insufficient to adequately suppress joint damage progression in these patients.

INTRODUCTION

Anti-citrullinated protein antibodies (ACPA) are highly specific antibodies for rheumatoid arthritis.[1] Patients positive for ACPA have been shown to have higher disease activity,[2,3] worse functional ability[4,5] and more joint damage[2,3,6,7] in observational and/or non-disease activity-steered studies. ACPA-positivity was found to be predictive of not achieving remission.[8] ACPA-negative and ACPA-positive RA may be different diseases with different risk factors and clinical course and may require different therapeutic strategies.[9-11] Possibly ACPA-positive and ACPA-negative patients also respond differently in a tight control treatment strategy where medication is adjusted based on the aim of achieving low disease activity. Therefore, we compared the changes in Disease Activity Score (DAS), functional ability and radiological damage over time in ACPA-positive and ACPA-negative patients with early RA treated according to the same disease activity steered protocol.

METHODS

Patients

Eight-year follow-up data of all 484 patients with known ACPA-status included in the BeSt (Dutch acronym for Behandel Strategieën, "treatment strategies") study were analyzed. This is a multi-center randomized trial designed to compare four treatment strategies in 508 patients with recent-onset RA; initial monotherapy, step-up combination therapy (both starting with methotrexate monotherapy for ≥6 months), initial combination therapy with methotrexate, sulfasalazine and prednisolone and initial combination therapy with methotrexate and infliximab. Treatment was assessed every 3 months and adjusted if the DAS was >2.4. If the DAS was ≤2.4 for ≥6 months, medication was tapered to monotherapy in maintenance dose. Starting 2 years after inclusion, patients on monotherapy maintenance dose, who were in remission (DAS <1.6) for ≥6 months, stopped the last disease modifying anti-rheumatic drug (DMARD). Treatment was restarted if the DAS increased to ≥1.6. A more detailed description of the study protocol was published previously.[12]

Study endpoints

ACPA-status was determined with the CCP2 test using baseline sera (n=119) and sera collected during the first years of follow-up (n=365). The DAS and Health Assessment Questionnaire (HAQ) were used to assess treatment response. Drug-free remission was defined as a DAS <1.6 and not using any DMARD. All available radiographs of hands and feet at year 0-1-2-3-4-5-6-7-8 were scored using the Sharp-van der Heijde score

(SHS) by two independent readers, blinded for patient identity and time order (inter-observer intraclass correlation coefficient 0.96), to assess joint damage. For DAS and DAS components, areas under the curve (AUC) were calculated, only for years with complete data. For years with ≤2 missing values, the last observation carried forward was used to calculate the AUC, to avoid exclusion of these data.

Statistical analysis

Baseline characteristics and clinical parameters were compared using the χ^2 test, Student's t test or Mann-Whitney U test. HAQ and DAS components over time were compared using linear mixed models with ACPA-status and time as categorical variables and HAQ or DAS component respectively at baseline, adjusted for baseline gender, smoking habits, age and SHS with a Toeplitz covariance structure. Spearman's correlation coefficient test was used to analyze the correlations after 8 years. ORs for achieving (drug-free) remission, of restarting medication and of joint damage progression were calculated for ACPA-positive patients using logistic regression analyses, adjusted for gender, smoking habits, baseline age, DAS and SHS. ORs were converted to RRs to find a more accurate estimation of the effect size.[13]

To examine the influence of treatment strategy, we used generalized estimating equations with an auto-regressive covariance structure, time as categorical variable, baseline SHS, DAS, age, gender, smoking habits, ACPA-status, treatment strategy and ACPA*treatment strategy with yearly damage progression as outcome. To assess the possible difference in the association between disease activity and joint damage progression for ACPA-positive and -negative patients, we used generalized estimating equations with these components but with treatment strategy replaced by yearly AUC DAS or AUC DAS component (with baseline DAS component instead of baseline DAS).

RESULTS

Treatment response

ACPA-positive patients had a lower baseline DAS and HAQ and a higher SHS. Disease activity over time was similar in both ACPA-groups.(*figure 1a*) Functional ability was not different for ACPA-positive and ACPA-negative patients (p=0.9).(*figure 1b*) This similar treatment response in both ACPA-groups was seen both in patients initially treated with methotrexate monotherapy and with combination therapy (p=0.8 and p=0.9).(*figure S1*) ACPA-positive patients did have a significantly higher (4.5mm/hr) erythrocyte sedimentation rate (ESR).(*figure 1c*) Disease activity and functional ability showed a moderate correlation after 8 years: rs:0.5 (p<0.001). The rates of achieving remission at least once or of ≥1 year consecutively were not different: RR of 1.0 (95% CI 0.9;1.1) and 0.9 (95% CI

0.7;1.1), respectively. ACPA-positive patients were less likely to achieve drug-free remission, with a RR of 0.4 (95% CI 0.3;0.7) and more likely to lose remission and having to restart DMARD: RR 2.3 (95% CI 1.4;3.0). Similar results were seen for patients who were both ACPA and RF positive or negative.

The median number of treatment steps (2 (IQR 1-4) vs 1 (IQR 1-4)) that patients had failed on and the proportions of patients who had dropped out before year 8 were not significantly different for ACPA-positive and ACPA-negative patients in the whole cohort, or when stratified for initial treatment strategy.

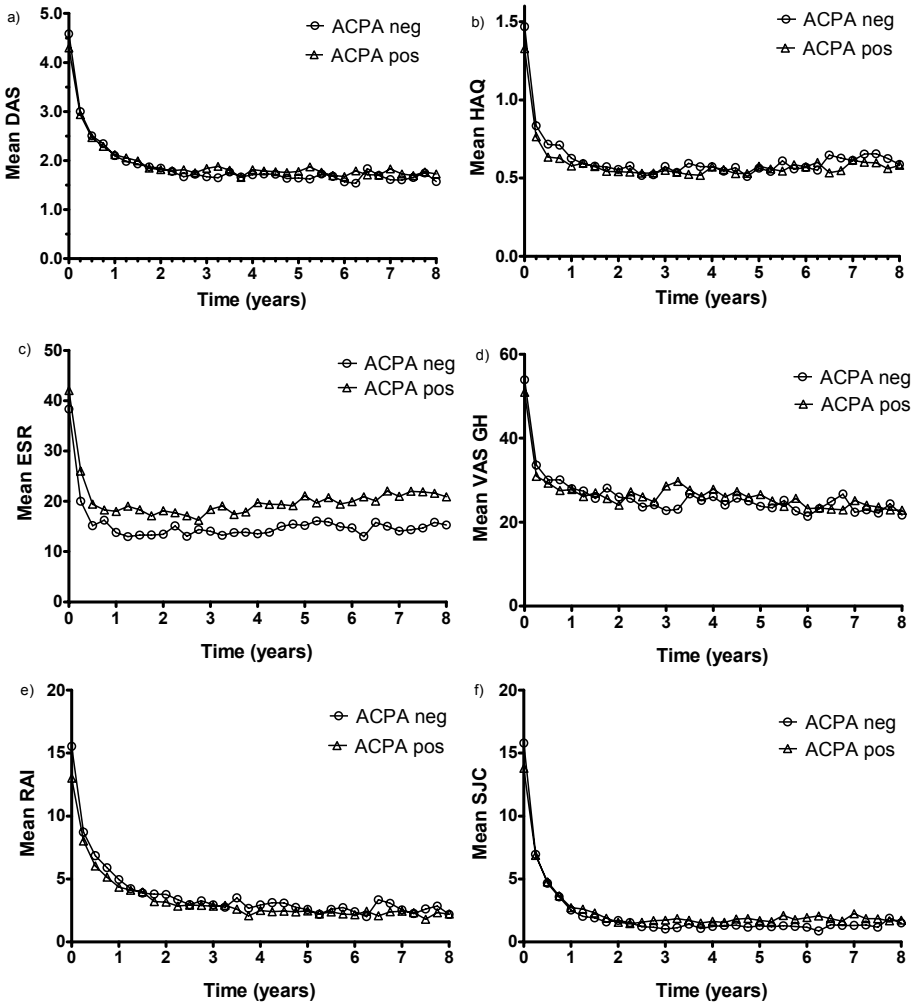

Figure 1: DAS (a), HAQ (b), erythrocyte sedimentation rate (ESR) (c), patient visual analogue scale global health (VAS) (d), Ritchie Articular Index (e) and Swollen Joint count (f) over 8 years for anti-citrullinated protein antibody (ACPA)-positive and ACPA-negative patients

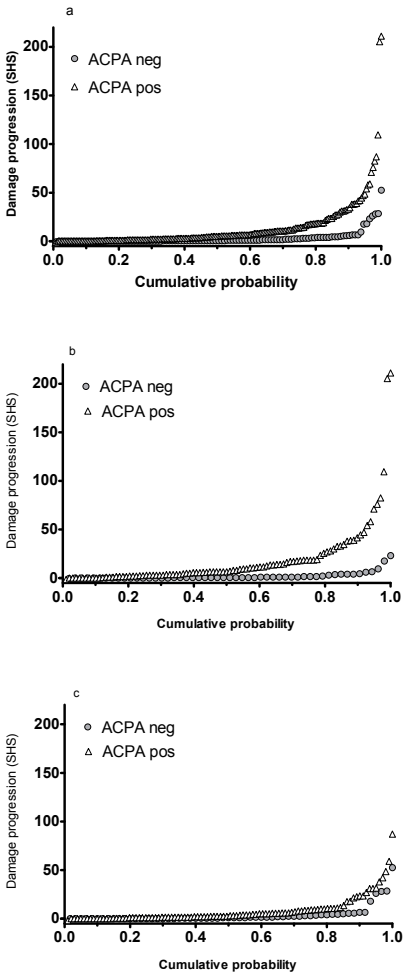

Figure 2: Probability plots of joint damage progression over 8 years for anti-citrullinated protein antibody (ACPA)-positive and ACPA-negative patients, (A) all patients, (B) initial treatment monotherapy (groups 1 and 2), (C) initial combination treatment (groups 3 and 4)

Joint damage progression

ACPA-positive patients showed more radiological damage progression than ACPA-negative patients.(*figure 2a*) The RR for progression >5 points (SHS) was 3.8 (95% CI 2.5;5.0), 3.7 (95% CI 1.9;6.3) for >15 points, 3.2 (95% CI 1.4;6.4) for >25 and 6.2 (95% CI 1.5;20.3) for >35 points. Similar results were seen for patients who had been in remission for ≥1 year (*figure S2*) and for patients who were both ACPA and RF positive or negative. ACPA was a predictor of joint damage progression independent of RF.

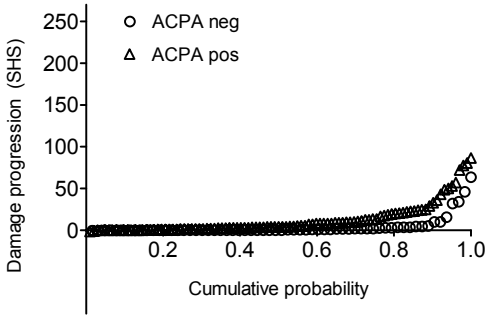

Figure S2: Probability plot of joint damage progression over 8 years for anti-citrullinated protein antibody (ACPA)-positive and ACPA-negative patients who have been in remission for ≥1 year consecutively

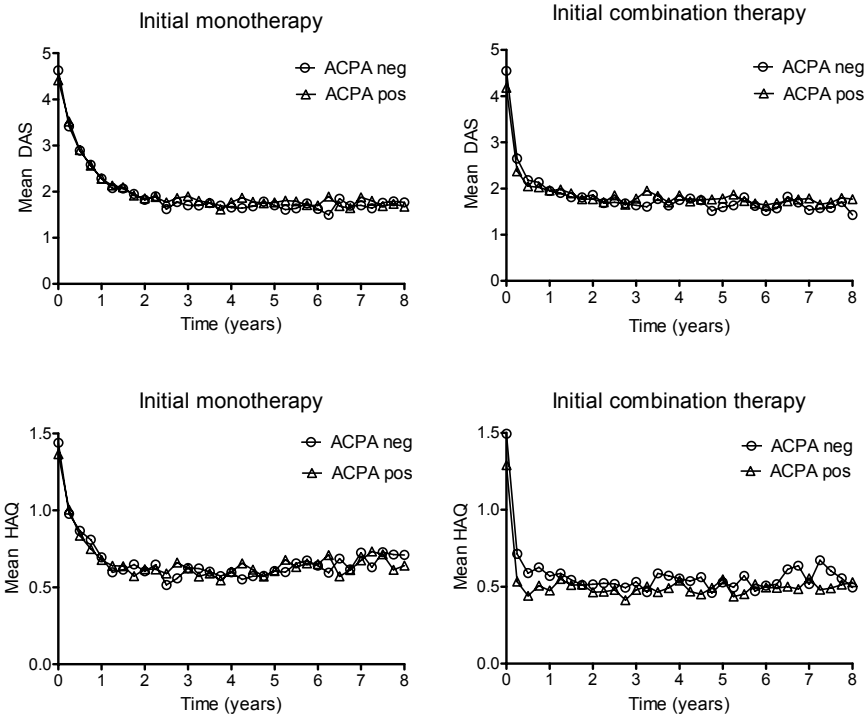

Figure S1: DAS and HAQ over 8 years for anti-citrullinated protein antibody (ACPA)-positive and ACPA-negative patients

The association of ACPA-status with joint damage progression was significantly influenced by initial treatment strategy (monotherapy or combination treatment).(*figures 2b,2c*) The difference in SHS between ACPA-positive and -negative patients initially treated with combination therapy was 1.7 points smaller than the difference in SHS for ACPA-positive and -negative patients initially treated with monotherapy ($p<0.001$). Second, the association was influenced by disease activity. ACPA-positive patients showed 1.8 points more increase in SHS per point of the DAS ($p=0.001$), 0.1 points per mm/hr ESR ($p=0.003$), 0.2 per tender joint ($p=0.02$) and 0.1 per swollen joint ($p=0.005$). The association with VAS global health was not influenced by ACPA-status. Joint damage and functional ability at year 8 did not show a significant correlation.

DISCUSSION

Response to DAS-targeted treatment was similar in ACPA-positive and ACPA-negative patients in terms of reduction of disease activity including remission percentages, and improvement of functional ability, although ACPA-positive patients had a higher ESR over time. ACPA-positive patients did show more joint damage progression, in particular in patients treated with initial methotrexate monotherapy. ACPA-positivity also was a predictor for not achieving and for losing drug-free remission.

To our knowledge, we are the first to report on disease activity in ACPA-positive and ACPA-negative patients in a disease activity steered treated cohort. In previous non-disease activity steered studies of patients with similar disease duration, ACPA-positive patients did show higher disease activity.[2,3] In a study of 273 patients with recent-onset RA with 6 years of follow-up,[7] similar functional ability was found for ACPA-positive and ACPA-negative patients after correction for disease activity and RF, but ACPA-positive patients had more joint damage, which is in line with our results. The relatively short follow-up period may account for these findings, as radiological joint damage shows a weak correlation with functional ability in the first years after the diagnosis of RA, but a moderate correlation after 12 years, while disease activity shows a stable, moderate correlation with functional ability from baseline onwards.[14] In our tight controlled cohort we found a moderate correlation between functional ability and disease activity but no significant correlation with radiological joint damage after 8 years. Longer follow-up will show whether radiological joint damage will significantly contribute to functional disability with longer disease duration.

Our observation that ACPA-positivity is a predictor for not achieving drug-free remission and for relapsing if drug-free remission was achieved, is an extension on similar results after 5 years of treatment.[15] The results are also in line with the findings of Balsa *et al*,[5] who found that ACPA-positivity was a predictor for not achieving drug-free remission for

≥5 years, and of van der Woude *et al.*[16] who found that ACPA-positivity was a predictor for not achieving drug-free remission for ≥1 year. It might be wise to take ACPA-status into consideration when contemplating cessation of medication.

In conclusion, DAS-targeted therapy is equally effective in reducing disease activity, achieving remission and improving functional ability in ACPA-positive and ACPA-negative patients with recent-onset RA. Still, ACPA-positive patients had more radiological damage, especially patients initially treated with methotrexate monotherapy. This suggests that in ACPA-positive patients, initial methotrexate monotherapy is insufficient to suppress joint damage progression even if subsequent treatment is DAS-targeted. This is in line with our previous findings[17,18] and the European League against Rheumatism recommendations, which suggest that in patients with poor prognostic factors such as ACPA-positivity, starting with combination therapy might be considered.[19] It may also mean that for ACPA- positive patients, the target of DAS ≤2.4 might not be stringent enough. The differences in joint damage progression and systemic inflammation indicate that the inflammatory mechanisms in ACPA-positive and ACPA-negative RA might have different mediators.

Table 1: baseline characteristics for ACPA-negative and ACPA-positive patients and drop-out at year 8

	ACPA – N=184	ACPA + N=300	p-value
Male gender (%)	48 (26)	111 (37)	0.013
Age (mean, SD)	55 (15)	54 (13)	0.5
Smoker (%)	51 (28)	117 (39)	0.012
RF pos (%)	59 (32)	258 (86)	<0.001
Treatment strategy (%)			0.2
Sequential monotherapy	40 (22)	80 (27)	
Step-up combination therapy	45 (25)	69 (23)	
Initial combination therapy with pred	56 (30)	68 (23)	
Initial combination therapy with IFX	43 (23)	83 (28)	
Symptom duration, wks (median, IQR)	22 (13-41)	25 (14-56)	0.06
DAS (mean, SD)	4.6 (0.9)	4.3 (0.8)	<0.001
HAQ (mean, SD)	1.5 (0.7)	1.3 (0.7)	0.02
SHS (median, IQR)	1.5 (0.0-6.1)	4.0 (1.0-10.5)	<0.001
Number of treatment steps failed on before year 8 (median, IQR)	1 (1-4)	2 (1-4)	0.2
Drop-out at year 8	54 (29)	84 (28)	0.7

ACPA Anti-Citrullinated Protein Antibodies *RF* Rheumatoid Factor *DAS* Disease Activity Score *HAQ* Health Assessment Questionnaire *SHS* Sharp-van der Heijde Score

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Chapter 6

High BMI is associated with decreased treatment response to combination therapy in recent onset RA patients- a subanalysis from the BeSt study

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ABSTRACT

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

Methods In the BeSt study, 508 patients were randomized to initial monotherapy or combination therapy with prednisolone or infliximab (IFX). Response to disease activity score (DAS)≤2.4- steered treatment (first dose and after 1 year) was compared between patients with a BMI <25 and ≥25, using relative risk regression analyses. DAS, components of DAS and functional ability during the first year were compared using linear mixed models.

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

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

INTRODUCTION

An association between treatment response to TNF-blockers and BMI was described in a group of patients with established RA who had failed on disease modifying anti-rheumatic drugs (DMARD) treatment. Patients with a high BMI responded less well to treatment with a fixed dose of TNF-blocker infliximab (IFX).[1] This finding was replicated in patients who had failed on methotrexate and were treated with a fixed dose of adalimumab, etanercept or infliximab.[2] Patients with a high BMI and thus a higher fat mass might show more inflammation.[3,4] Yet, clinical synovitis might be less easy to assess in RA patients with a high BMI. It has also been described that patients with various conditions and a high BMI report more pain than patients with normal or low BMI.[5-7]
In the BeSt trial, a treat to target trial in early RA patients, treatment response in terms of Disease Activity Score (DAS) and patient reported outcomes was assessed every 3 months and yearly radiographs were taken. Because different treatment strategies were used, we could analyze the association between BMI and different components of treatment response not only to TNF-blockers, but also to conventional DMARD mono- or combination therapy.

METHODS

Patients from the BeSt cohort, a study originally designed to compare four different treatment strategies in early DMARD-naïve rheumatoid arthritis patients, were analyzed. Patients were randomized to sequential monotherapy (group 1) or step-up combination therapy (group 2) starting with methotrexate (MTX), initial combination therapy (group 3) with the COBRA scheme: MTX, sulfasalazine (SSA) and high dose tapered prednisolone or a combination of MTX and IFX (group 4).
Treatment was a disease activity score (DAS)-steered and aimed at a DAS≤2.4 resulting in treatment adjustments every three months as long as the DAS was >2.4. Thus, In groups 1-3, delayed infliximab treatment was initiated if patients had failed on at least 3 synthetic DMARD, including methotrexate, sulfasalazine, leflunomide (in arm 1) or hydroxychloroquine (in arm 2) and prednisolone (in arms 2 and 3). In all arms, DMARD treatment was changed or added to at least twice in case of insufficient response (DAS>2.4), before MTX+IFX combination therapy was started. Patients treated with MTX+IFX started IFX in a dose of 3 mg/kg/8weeks, but if the DAS remained >2.4, the IFX dose was escalated from 3 mg/kg/2 months to 6, 7.5 and finally 10 mg/kg if necessary. If the highest dose did not lead to a low DAS, MTX+IFX were abandoned and the next treatment initiated. At any stage of the protocol, if patients achieved a DAS≤2.4 for ≥6 months, treatment was tapered to maintenance dose: MTX monotherapy in groups 1

and 2, sulfasalazine monotherapy in group 3 and MTX+IFX 3mg/kg/2 months in group 4. More details on the treatment protocol were published previously.[8]

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

Statistical analysis

Statistical analyses were performed with the software program SPSS version 17.0 and STATA 12. Baseline characteristics were compared between patients with normal and high BMI, using the Student's t test, Mann Whitney U test or Chi square test. To determine whether a higher BMI was associated with impaired response to therapy according to the definitions above, a relative risk regression model was used, where the parameters were estimated using a modified Poisson regression approach with robust standard errors.[10] These analyses give risk ratios, which are easier to interpret than odds ratios. The analyses were adjusted for gender, age, smoking habits, rheumatoid factor (RF) and baseline DAS. Then the regression analyses for treatment response were repeated stratified for treatment group (groups 1&2, group 3 and group 4). The association between BMI and failure to achieve a DAS≤2.4 on delayed IFX was examined in patients from group 1-3 who received MTX+IFX after failing on several DMARD. Differences in baseline characteristics in this group, associated with response to DMARD, were observed between patients with low or normal and high BMI, indicating that there might be a selection bias. Therefore propensity scores, with age, RF, alcohol use (yes/no), treatment group, baseline ESR, number of swollen joints, visual ana-

logue scale global and morning stiffness (VAS) as predictors and high BMI as outcome were calculated using logistic regression. Then to correct for the differences between patients with normal and high BMI, a relative risk model was fitted with the weighting based on the estimated propensity score, i.e. 1/propensity score for patients with high BMI and 1/(1-propensity score) for patients with normal BMI. Weights larger than 5 were truncated at 5. We repeated the analyses with BMI as a (linear) continuous variable. There was no evidence of a non-linear association (tested by comparing likelihoods of different models and by using fractional polynomials). To find out whether there was a difference in disease manifestation in the first year of treatment, between the BMI categories in the various DAS components or in patient reported outcomes, linear mixed models were fitted. The following dependent variables were used in the different models: tender joint count, swollen joint count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), patients' assessment of global health (VAS global), and of pain (VAS pain) and Health Assessment Questionnaire (HAQ) score. In each of the models time and BMI category were entered as categorical covariates and the baseline value of the dependent variable as continuous covariate. The interaction between time and BMI was not significant in any of the analyses, therefore it was not included in the final models. The estimates were adjusted for gender, age, RF and smoking habits.
The number of treatment steps patients had failed on after 8 years was compared using the Mann Whitney U test.

RESULTS

Patients with a BMI≥25 were older than patients with a BMI<25: 56 versus 53 years (p=0.03) and were less often smokers (31 versus 41%, p 0.01).(*table 1*) No other significant differences in baseline characteristics were observed. A BMI ≥30 was observed in 15% of all patients.
High BMI was an independent predictor of failing (not achieving a DAS ≤2.4) on the first treatment step with a RR of 1.20 (95% CI 1.05;1.37).(*table 2*) A minor effect was observed for failing on treatment steps in year 1 (step 1 and 2 in groups 1-3 or steps 1, 2 and 3 in group 4) with a RR of 1.15 (95% CI 0.92;1.43). Analyses were repeated with BMI as a continuous variable and these results confirm the findings of the dichotomized analyses. High BMI was again an independent predictor of failing on the first step (RR 1.03, 95% CI 1.01;1.06) and for failing on treatment steps in year 1 (RR 1.02, 95% CI 1.01;1.04).(*table 3*)
After 8 years of DAS-targeted treatment, the median (IQR) number of treatment steps patients had failed on was 1 (0-3) for patients with a BMI<25 and 2 (1-4) for patients with a BMI≥25, p<0.001. The percentage of patients who after 8 years were no longer treated according to protocol due to failing on all treatment steps was not different: 26% vs 22%, p=0.4.

Table 1: baseline characteristics for patients with normal and high BMI

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

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

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

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

First dose: MTX monotherapy in groups 1 and 2, MTX+sulfasalazine+prednisolone in group 3, MTX+infliximab in group 4
Year 1: failing on treatment step 1 and 2: methotrexate monotherapy (15 or 25 mg/week) in groups 1 and 2, on combination therapy with prednisolone (methotrexate 7.5 or 25 mg/week) in group 3, and on treatment steps 1, 2 or 3 (methotrexate 25 mg/week plus infliximab increased from 3, 6 to 7.5mg/kg/2 months) in group 4
Reference: patients with a BMI <25
*adjusted for gender, age, smoking habits, rheumatoid factor (RF) and baseline DAS
** p-value <0.05
Data are presented as RR (95% CI)

Table 3: risk of not achieving a DAS ≤2.4 (on the first dose and during year 1) in patients with a high BMI (BMI as continuous variable)

	Crude RR	Adjusted RR*
Fail on initial treatment step (all)	1.03 (1.01;1.04)**	1.02 (1.01;1.04)**
Fail on first dose MTX monotherapy	1.02 (1.002;1.03)**	1.02 (1.003;1.03)**
Fail on initial dose MTX+SSA+prednisolone	1.05 (1.01;1.09)**	1.05 (1.01;1.09)**
Fail on initial dose MTX+infliximab	1.03 (0.99;1.07)	1.03 (0.99;1.07)
Fail in year 1 (all)	1.03 (1.008;1.06)**	1.03 (1.005;1.06)**
Fail in year 1 (groups 1+2)	1.02 (1.002;1.04)**	1.02 (0.998;1.04)**
Fail in year 1 (group 3)	1.06 (0.97;1.17)	0.99 (0.99;1.16)
Fail in year 1 (group 4)	1.04 (0.97;1.11)	1.04 (0.98;1.11)

Legend of table 2 also applies to this table

Treatment groups

In groups 3 and 4, a higher risk of impaired response to therapy for patients with a high BMI was found with RRs of 1.55 (95% CI 1.06;2.28) and 1.42 (95% CI 0.98;2.06) for response to the first dose. For group 3, the RR for response to the first 2 treatment steps in year 1 was 1.46 (95% CI 0.75;2.83). The effect of impaired response in patients with a high BMI was stronger in group 4: RR 2.20 (95% CI 0.99;4.92). In groups 1 and 2, no significant association between treatment response and BMI was observed.

Delayed infliximab

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

However, in crude analyses no association was seen between BMI and response to treatment in patients from groups 1-3 who received delayed MTX+IFX: RR 1.11 (95% CI 0.71;1.73) for response to first dose, and a trend was seen for response after 1 year: RR 1.56 (95% CI 0.80;3.04). After adjusting for the misbalance in the baseline characteristics using propensity weighing the RR of failure to the first dose changed to 1.37 (95% CI 0.81;2.31), the RR of failure after 1 year to 2.09 (95% CI 0.97;4.49).

Disease activity components

In year 1, adjusted for baseline differences, patients with high BMI had higher disease activity (difference in DAS 0.30 (95% CI 0.15;0.45)), a higher HAQ score (difference 0.14

(95% CI 0.05;0.23)) and a higher VAS pain (difference 6.2 mm (95% CI 3.0;9.4)). For DAS components, a difference was found in tender joints (difference 1.4 (95% CI 0.6;2.2)) and patient's assessment of global health (difference 4.9 mm (95% CI 1.9;7.8)), but not for swollen joints (difference 0.6, 95% CI -0.02;1.2).(*table 4, figure 1*) Radiological damage progression in year 1 and over 8 years follow up was similar in patients with high or low/normal BMI: median progression.(*figure 2*)

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

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

DAS Disease Activity Score, *HAQ* Health Assessment Questionnaire score, *VAS* visual analogue scale, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *TJC* tender joint count, *SJC* swollen joint count
*Adjusted for rheumatoid factor, age, gender and smoking habits
Data are presented as β-estimate (95% CI)

DISCUSSION

In this DAS-targeted treated cohort with early RA patients, high BMI was associated with failure to achieve a low DAS (≤2.4) on anti-rheumatic therapy, also after adjustment for confounders. This was most noticeable in patients who were treated with initial combination therapy with methotrexate, either combined with prednisolone and sulfasalazine, or with infliximab. The association between high BMI and failure on treatment remained if the dose of methotrexate or infliximab was increased. After stratification for initial therapy (initial monotherapy with MTX in groups 1-2, initial combination therapy with MTX, sulfasalazine and prednisolone in group 3 or MTX and infliximab in group 4), patients with a high BMI who were treated with initial combination therapy were more likely to show a decreased response to treatment than patients with a normal BMI. This association was still seen after 1 year, after failure on the initial treatment had led to dose increases (of methotrexate in group 3 and of infliximab in group 4), but less so in group 3 than in group 4. High BMI was also associated with failure to achieve a low DAS on delayed treatment with infliximab, in patients who had failed on at least 3 conventional

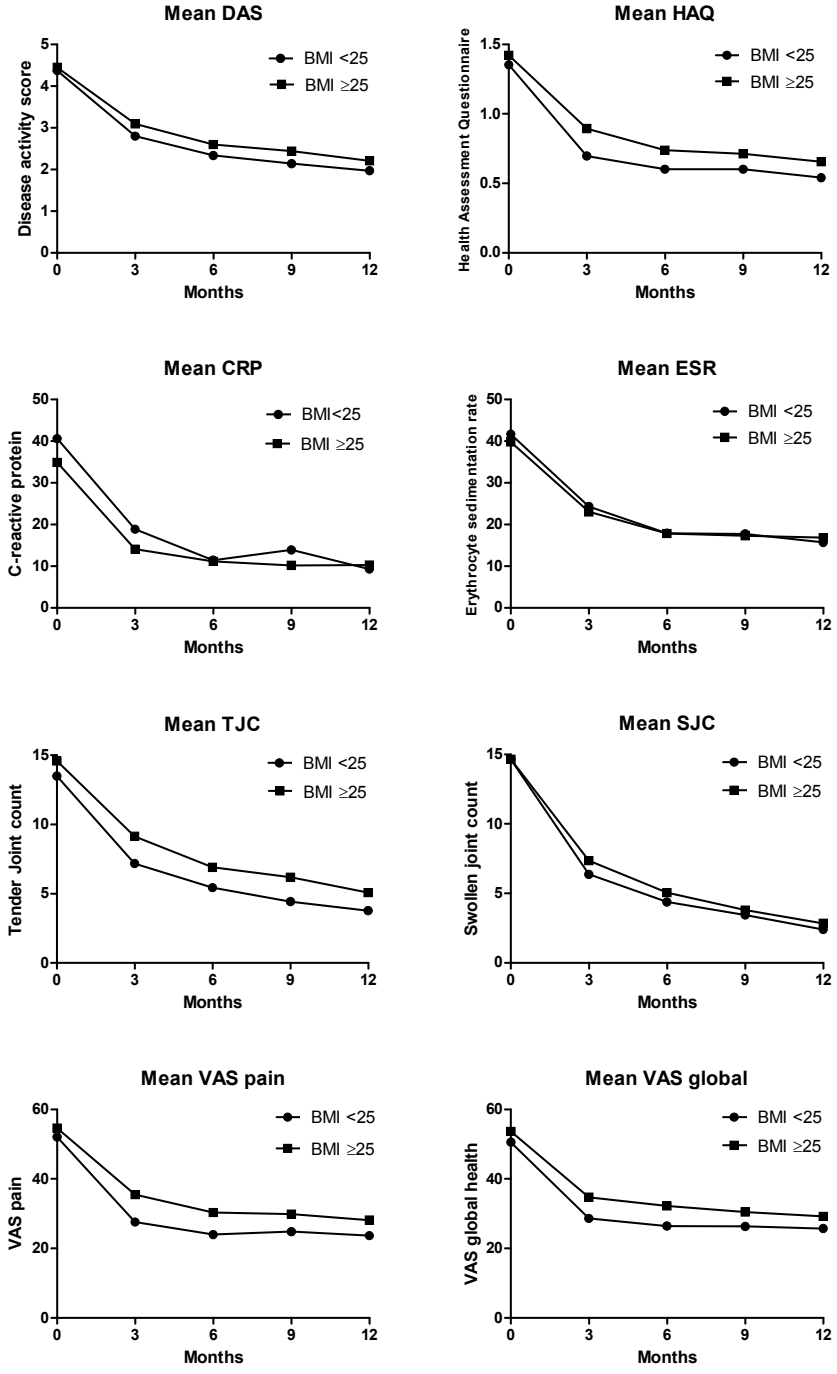

Figure 1: Disease Activity Score, Health Assessment Questionnaire, VAS global health, Erythrocyte sedimentation rate, Tender joint count, Swollen joint count, patient's assessment of pain (on a visual analogue scale) and physician's assessment of disease activity in year 1 for patients with a BMI<25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

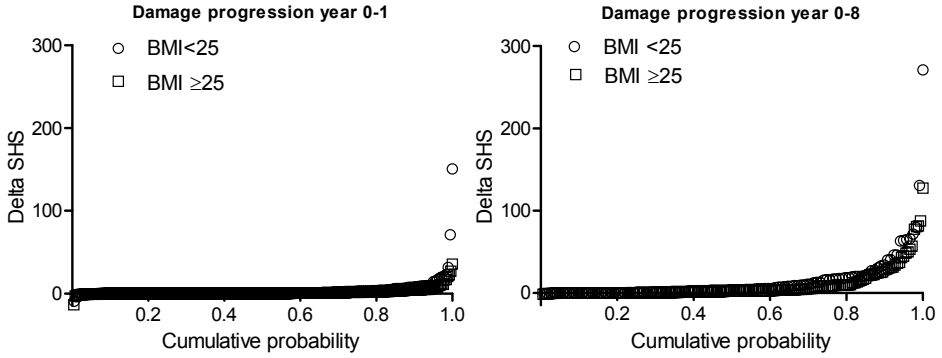

Figure 2: Cumulative probability plot of joint damage progression in year 0-1 and in years 0-8 for patients with a BMI<25 and ≥25

DMARD. Due to more failure to achieve a low DAS on treatment, patients with high BMI went through significantly more treatment steps over 8 years of DAS-targeted treatment than patients with low/normal BMI. Failure to achieve a low DAS depended mainly on the pain and joint tenderness scores, which were higher in the patients with a high BMI, whereas joint swelling and laboratory parameters of inflammation were similar in patients with high or low/normal BMI.

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

Rather than being the result of high ESR or swollen joint counts, the higher DASs scored in patients with higher BMI appear to depend on pain. Higher pain scores and worse global health were also reported in patients with a high BMI in a large Swedish cohort.[13] There, patients with a BMI≥30 also had a higher ESR and CRP at follow up. We found no

association between a high BMI and higher parameters of inflammation or more joint swelling, but there were very few patients with a BMI≥30.

It is possible that we underestimated joint swelling in patients with a high BMI.[14] The higher tender joint counts in patients with a high BMI might still reflect more local inflammation. We previously reported that local joint tenderness is a predictor of local joint damage after 1 year, independent of swelling.[14] This in fact supports the practice of using a composite score such as the DAS as treatment target, not merely joint swelling. We found no differences in joint damage progression after 8 years of DAS-targeted treatment in patients with high or low/normal BMI. This may be due to more treatment adjustments (because of higher DAS) in patients with high BMI, or there may be another reason why patients with high BMI appear to be protected against joint damage progression.[15,16] It may also be that the pain experienced by patients with high BMI does not reflect inflammation. We did not do routine assessments of fibromyalgia features, but we cannot exclude that a fibromyalgia component was present in part of these patients. Self-reported pain, especially musculoskeletal pain, is higher in patients with a high BMI, in particular with a BMI≥30, and they are more likely to report pain in multiple locations.[5,6] The mechanism of the relationship between obesity and pain is unclear but it is suggested that disturbances in neurotransmitters and hormones might be, at least partially, responsible.[7] This relation between BMI and pain may also influence the association between high BMI and functional disability, which was found in this cohort. Pain and body size itself may both interfere with the daily activities that are listed in the Health Assessment Questionnaire.[17]

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

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

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

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

SD standard deviation, *BMI* body mass index, *ACPA* anti-citrullinated protein antibodies, *RF* rheumatoid factor, *DAS* disease activity score, *HAQ* health assessment questionnaire score, *SHS* Sharp-van der Heijde Score, *IQR* interquartile range, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *TJC* tender joint count, *SJC* swollen joint count, *VAS* visual analogue scale

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Chapter 7

Discontinuation of infliximab and potential predictors of persistent low disease activity in patients with early rheumatoid arthritis and DAS steered therapy: subanalysis of the BeSt study

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ABSTRACT

Objective To describe the disease course after discontinuation of infliximab (IFX) in early rheumatoid arthritis patients with DAS steered treatment and to identify predictors of persistent low disease activity.

Methods In a post hoc analysis of the BeSt study, we observed disease activity and joint damage progression in patients treated with methotrexate (MTX)+IFX, who discontinued IFX after achieving low disease activity (DAS ≤2.4), for 6 months. We identified predictors using Cox regression analysis.

Results 104 patients discontinued IFX, of whom 77 had received IFX+MTX as the initial treatment. Mean DAS at time of IFX discontinuation was 1.3, median symptom duration was 23 months and median Sharp-van der Heijde score was 5.5. The median follow-up was 7.2 years. IFX was reintroduced after loss of low disease activity in 48%, after a median period of 17 months. Joint damage progression rate didn't increase in the year after discontinuation, regardless of flare. After reintroduction of IFX, 84% of these patients again achieved a DAS ≤2.4. In the multivariable model smoking, IFX treatment duration ≥18 months and shared epitope (SE) were independently associated with reintroduction of IFX: 6% of the non-smoking, SE negative patients treated <18 months needed IFX reintroduction.

Conclusion Discontinuation of IFX was successful in 52%, with numerically higher success rates in patients initially treated with IFX. Of the 48% who flared, 84% regained low disease activity. Joint damage progression rate didn't increase in the year after discontinuation. Smoking, long IFX treatment duration and SE were independently associated with reintroduction of IFX.

INTRODUCTION

Current RA treatment strategies are aimed at achieving low disease activity as soon as possible, to improve structural and functional outcome, using frequent treatment adjustments when necessary. Adding a TNF-blocker to methotrexate (MTX) has proved to be an effective way to achieve low disease activity in a short period of time, with less joint damage progression than monotherapy.[1,2]

Treatment with TNF-blockers is expensive and has a possible risk of adverse events. Therefore, discontinuation of TNF-blockers once the treatment goal has been achieved could be beneficial for both society and individual patients. In 25-70% of patients who achieved low disease activity, TNF-blockers can be stopped without losing low disease activity.[3-7] Predicting which patients have a high chance of sustained low disease activity after discontinuation of TNF-blockers is necessary to avoid disease flares and a potentially increased risk of infusion reactions after reintroduction of intravenous TNF- blockers.[8]

In the BeSt study, a study comparing 4 different treatment strategies, infliximab (IFX) was the TNF-blocker used in combination with MTX, either after failure on at least three non-biological DMARD, or as initial treatment. In this post hoc analysis with a median follow-up duration of 7.2 years, we investigated whether and how often low disease activity was sustained after discontinuation of IFX and if predictors for successful discontinuation exist. Secondly, we looked at joint damage progression after IFX discontinuation and we assessed the success and safety of reintroduction.

METHODS

Patients

Between 2000 and 2002, 508 patients were included in the BeSt study, a multi-center randomized single blind clinical trial designed to compare 4 different treatment strategies in DMARD-naïve patients with recent onset, active RA. All patients fulfilled the 1987 ACR inclusion criteria for RA. The ethics committees of all participating centers approved the study protocol and patients gave their written informed consent.

Treatment strategies were initial monotherapy, step-up combination therapy (groups 1 and 2, both starting with MTX), initial combination therapy with MTX, sulfasalazine and prednisolone (group 3) and initial combination therapy with MTX and IFX (group 4). Treatment was adjusted to the next step in the protocol in case of a DAS >2.4 or side effects.

In group 1-3, MTX+IFX were started after patients had failed on 3 treatment steps with non-biological DMARD including prednisolone (groups 2 and 3) or without (group 1). If DAS remained ≤2.4 for at least 6 months, IFX was stopped, after stepwise (10-7.5-6-3)

tapering to 3 mg/kg/8 weeks in those patients who had previously had a dose increase. IFX was immediately restarted if the DAS increased to >2.4. In patients who had also tapered or stopped methotrexate, first MTX was increased to 25 mg/week. Next, IFX was reintroduced if the DAS remained >2.4.The complete study design has been published previously.[9,10]

We analyzed all 104 patients in groups 1-4 who discontinued IFX after the DAS was ≤2.4 for 6 months, who had ≥1 year of follow-up after reaching this point. The median follow-up duration from the moment of IFX discontinuation was 7.2 years (range 14-103 months).

Study endpoints

After discontinuation of IFX, whether patients had to restart IFX due to a DAS >2.4 was monitored. Radiographs of hands and feet were taken at yearly intervals. For the radiograph 'at discontinuation', the radiograph taken closest to the visit at discontinuation was used. For stop-visits in between 2 yearly visits, the yearly visit before discontinuation was chosen. All available radiographs of hands and feet, baseline-1-2-3-4-5 year follow-up were scored blind for patient identity and random in time using the Sharp-van der Heijde score (SHS). Joint damage progression in the year before and after discontinuation was defined as increase of the average score for those years of 2 independent readers. Smokers were defined as patients smoking cigarettes, cigars or pipe at baseline.

Statistical analysis

Baseline and disease characteristics were compared between patients from the initial and the delayed IFX treatment group, using the χ^2, Student's t or Mann-Whitney U test. Joint damage progression and HAQ scores were compared for patients with sustained DAS ≤2.4 and patients who had to restart IFX using the χ^2 and Mann-Whitney U test. To compare damage progression in the years before and after discontinuation and HAQ scores at and after discontinuation, the Wilcoxon signed-rank test was used. To take into account the difference in follow-up after discontinuation between patients, we used Cox regression analyses to identify predictors of successful discontinuation, after verifying that the proportional hazards assumption wasn't violated.[11] The dependent variable was time to reintroduction for patients who restarted IFX, August 1st 2010 for patients with sustained DAS ≤2.4 who were still under follow-up, and time to last follow-up visit for patients lost to follow-up.

We examined the association between baseline characteristics and clinical parameters at the moment IFX was stopped, with successful discontinuation of IFX. Because of the number of variables tested, we considered a $p<0.01$ significant.

To identify independent predictors, variables that showed an association ($p<0.10$) with sustained DAS ≤2.4 in the univariable analyses were entered in a multivariable Cox re-

gression analysis using a stepwise forward selection procedure with a Wald significance <0.05 as inclusion criterion. Subsequently, other variables that were hypothesized to have additional predictive value were added one by one. Model fit was tested using Martingale residuals. Overall goodness-of-fit was examined by adding to the model risk groups, constructed by categorizing the ranked prognostic indices, to test whether this would significantly improve the model likelihood.[11]

RESULTS

Low disease activity

IFX was discontinued after achieving a DAS ≤2.4 for ≥6 months in 104 patients (*figure 1*): 77/120 from the initial IFX treatment group and 27/109 from the delayed treatment group (p<0.001). The mean DAS at time of discontinuation was 1.3 ±0.6 (SD). The median IFX treatment duration was 11 (IQR 9-17) months. Median symptom duration at time of discontinuation was 23 (IQR 15-35) months. In 20 patients the IFX dose had been increased from 3 to 6, mg/kg, to 7.5, in 13 patients and to 10 mg/kg in 5 patients before a DAS ≤2.4 was achieved.

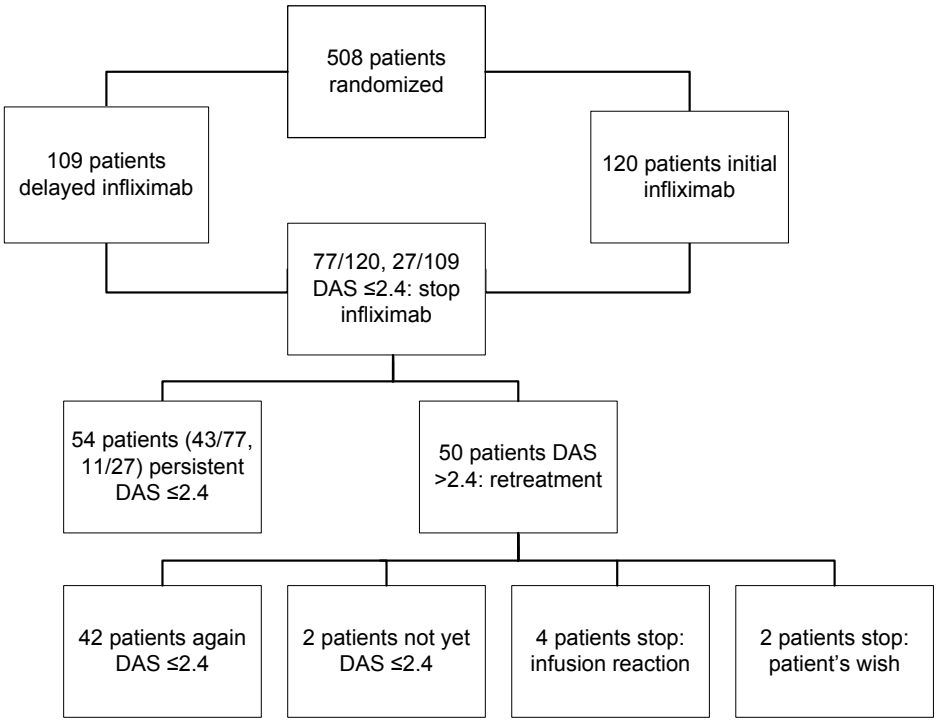

Figure 1: Flowchart of the study

After discontinuation of IFX, the DAS remained ≤2.4 in 43/77 patients (56%) from the initial treatment group and 11/27 (41%) from the delayed treatment group. MTX was then successfully tapered (with 2.5 mg every 4 weeks) to maintenance dose (≤10mg/week) in 34 (62%) patients, without differences between the initial and delayed treatment group (p=0.58). Subsequently, 15 (27%) patients from the initial treatment group achieved drug-free remission. None in the delayed treatment group achieved drug-free remission yet.

Treatment group

In the delayed treatment group, the median (IQR) time from baseline to starting IFX was 14 (11-18) months. Patients in the delayed treatment group had a higher baseline DAS and needed longer IFX treatment before IFX could be discontinued than patients in the initial treatment group. At the time of IFX discontinuation, patients in the delayed treatment group had longer symptom duration and a higher SHS, HAQ and patient's

Table 1: patients' demographic and disease characteristics at inclusion and at discontinuation of IFX in the initial versus delayed IFX treatment group

	All (n=104)	Initial (n=77)	Delayed (n=27)	p-value
Female gender, no. (%)	68 (65)	47 (61)	21 (78)	0.12
Age (years)	56 (46-61)	56 (45-61)	55 (50-62)	0.83
RF positive, no. (%)	68 (65)	45 (58)	23 (85)	0.012
ACPA-positive, no. (%)	76 (73)	56 (73)	20 (74)	0.89
SE positive, no. (%)*	66 (75)	48 (74)	18 (78)	0.67
Smoking +, no. (%)	36 (35)	22 (29)	14 (52)	0.029
BMI kg/m^2	26 (23-28)	26 (23-27)	26 (23-28)	0.59
Symptom duration at discontinuation, months	23 (15-35)	19 (13-27)	44 (33-64)	<0.001
IFX treatment duration at discontinuation, months	11 (9-17)	9 (8-14)	16 (11-23)	<0.001
DAS at inclusion, mean (SD)	4.2 (0.8)	4.1 (0.7)	4.7 (0.9)	<0.001
DAS at discontinuation, mean (SD)	1.3 (0.6)	1.3 (0.6)	1.4 (0.6)	0.50
Remission at discontinuation, no.(%)	69 (66)	51 (66)	18 (69)	0.78
HAQ at inclusion	1.3 (0.9-1.7)	1.3 (0.8-1.8)	1.1 (1.0-1.5)	0.72
HAQ at discontinuation	0.1 (0.00-0.6)	0.2 (0.0-0.5)	0.4 (0.1-0.9)	0.012
SHS at inclusion	3.5 (0.5-10.5)	4.8 (0.5-10.9)	1.5 (0.5-9.0)	0.40
SHS at discontinuation	5.5 (1.0-16.0)	4.8 (0.5-13.9)	13.0 (3.0-30.6)	0.029

RF rheumatoid factor, *ACPA* anti-citrullinated antibodies, *SE* shared epitope, *BMI* body mass index, *IFX* infliximab, *DAS* disease activity score, *HAQ* health assessment questionnaire, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *SHS* Sharp-van der Heijde score, *VAS* visual analogue scale, measured in mm

*SE had missing data for 16 patients

Data are presented as median (IQR), unless stated otherwise.

assessment of disease activity. There were almost twice as many smokers in the delayed treatment group.(*table 1*)

Reintroduction of IFX

In 50/104 patients (48%), IFX was restarted after the DAS had increased to >2.4 in median 17 (IQR 3-47) months. IFX was discontinued for ≥1 year in 29 patients (58%). In 84%, 27/34 from the initial and 15/16 from the delayed IFX treatment group, a DAS ≤2.4 was regained after reintroduction of IFX within median 3 (IQR 2-5) months. In 5 (10%) patients, who had initially had a good response to reintroduction, IFX was later abandoned for another DMARD. Five patients had an infusion reaction after reintroduction of IFX. These infusion reactions were reported as non-serious, but reason for 4 patients to discontinue IFX. In comparison, 8/120 patients from the initial treatment group (group 4) of the BeSt study had an infusion reaction during their first treatment with IFX (p=0.46). Serious infections (requiring hospital admission) occurred in 40/1000 patient-years after reintroduction of IFX, compared to 16/1000 patient-years during the first treatment with IFX and 10/1000 patient-years during discontinuation of IFX.

Joint damage

Radiographs 1 year before, in the year of, and 1 year after IFX discontinuation were available in 90/104 patients. Median damage progression was 0 both for patients who had an increase of the DAS to >2.4 in the first year after discontinuation and patients whose DAS remained ≤2.4 (p=0.56). The average damage progression did not increase in the year after discontinuation compared to the year before discontinuation: 0.0 (IQR 0.0-0.8) vs. 0.0 (IQR 0.0-1.5), p=0.06. Four patients showed radiographic progression >5.(*figure 2*) One of these patients had restarted IFX in that year, the other 3 continued to have a DAS ≤2.4 (mean AUC DAS 2.0 in that year).

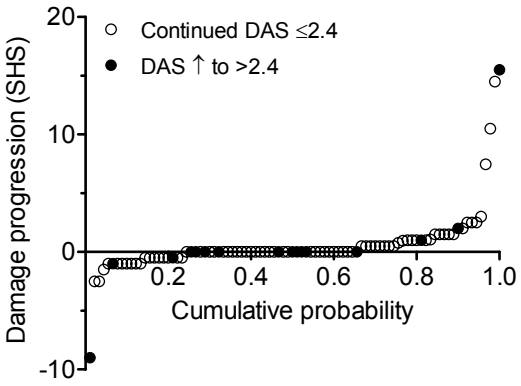

Figure 2: Probability plot of joint damage progression 1 year after discontinuation (90 patients with radiographic data)

Functional ability after discontinuation

HAQ scores at 1 and 3 years after discontinuation were similar to HAQ scores at discontinuation in both restarters and patients with sustained DAS ≤2.4. Five years after discontinuation, restarters had a median HAQ of 0.7, vs 0.3 at discontinuation, p-value=0.02. For patients with sustained DAS ≤2.4, median HAQ remained 0.1. Patients who flared in that year or the year before had higher median HAQ scores than patients who did not flare in those years: 0.4 vs. 0.1 in year 1, 0.5 vs. 0.1 in year 3 and 0.8 vs. 0.4 in year 5, but these differences were not significant.

Predictors

Univariable Cox analyses showed that smoking, longer symptom duration at discontinuation, longer IFX treatment duration, physician's assessment of disease activity, total erosion score at time of IFX discontinuation, and previous yearly change in SHS were associated with reintroduction of IFX.(*table 2*) Treatment timing (delayed vs initial IFX) and positivity for shared epitope (SE) showed a trend. Univariable analyses for the delayed and initial treatment group separately showed similar effect sizes, with the exception of smoking (lower hazard rate) and SE (higher hazard rate) in the delayed treatment group. (*table 2*) The multivariable analyses yielded a model with smoking, SE and treatment duration, adjusted for treatment timing. Treatment duration was dichotomized with 18 months (4th quartile) as cut-off value. The possible interaction between smoking and SE could not be assessed due to small numbers. Smoking (Hazard rate 2.1, 95% CI 1.1;4.2), treatment duration ≥18 months (HR 2.4, 95% CI 1.1;5.4) and presence of SE (HR 3.7, 95% CI 1.3;10.6) were independently associated with reintroduction of IFX.(*table 3*) IFX-free survival was investigated based on the number of predictors present.(*figure 3*) Of the 18% of patients who had no predictors present, 94% didn't need IFX reintroduction. Of the 40% who had 1 predictor present, 42% needed IFX reintroduction, compared to 67% of the patients with ≥2 risk factors. Because SE is rarely known in clinical practice and SE and anti-citrullinated protein antibody(ACPA)-status are highly correlated, we repeated the analyses using ACPA instead of SE. ACPA was not an independent predictor in the original model, or after omitting smoking. However, of the 18 patients who were non-smokers, had short treatment duration and were ACPA-negative, only 2 (11%) needed IFX reintroduction.(*figure 3D*)

Table 2: hazard rates for clinical and demographic parameters and increase of DAS to >2.4 with restart of IFX (univariable analysis)

	Hazard rate (95% CI)	Initial IFX	Delayed IFX
Female gender	1.1 (0.6;2.0)		
Age	1.00 (0.98;1.02)		
RF positive	1.2 (0.6;2.1)		
ACPA-positive	1.5 (0.8;3.1)	1.9 (0.8;4.5)	1.08 (0.3;3.4)
SE positive	3.9 (1.4;11.0)	3.2 (0.97;10.9)	7.0 (0.89;54.2)
Smoking	2.4 (1.4;4.3)	2.9 (1.5;5.8)	1.2 (0.4;3.2)
BMI	1.04 (0.96;1.12)		
IFX delayed	2.0 (1.1;3.7)		
Symptom duration, months	1.02 (1.01;1.03)	1.01 (0.99;1.03)	1.02 (0.995;1.05)
Treatment duration, months	1.05 (1.02;1.07)	1.07 (1.01;1.13)	1.03 (0.999;1.07)
IFX dose increase	1.2 (0.7;2.2)		
DAS	1.1 (0.7;1.9)		
DAS<1.6 vs DAS ≤ 2.4	0.98 (0.5;1.8)		
HAQ	1.5 (0.8;3.0)		
ESR	1.00 (0.98;1.02)		
CRP	0.98 (0.93;1.02)		
Tender joint count	1.08 (0.93;1.27)		
Swollen joint count	0.97 (0.77;1.22)		
Radiographic damage	1.02 (1.00;1.03)		
Erosion score	1.03 (1.01;1.06)	1.03 (0.99;1.07)	1.03 (0.99;1.07)
Joint space narrowing	1.03 (1.00;1.06)	1.03 (0.99;1.07)	1.02 (0.98;1.07)
Yearly change in SHS	1.07 (1.02;1.13)	1.08 (1.01;1.15)	1.06 (0.98;1.15)
Disease activity, VAS	1.01 (0.99;1.02)		
General health, VAS	1.00 (0.99;1.02)		
Morning stiffness, VAS	1.01 (1.00;1.02)		
Pain, VAS	1.01 (1.00;1.03)		
Disease activity, doctor VAS	1.03 (1.01;1.06)	1.03 (1.004;1.06)	1.09 (1.01;1.18)

RF rheumatoid factor, *ACPA* anti-citrullinated antibodies, *SE* shared epitope, *BMI* body mass index, *IFX* infliximab, *DAS* disease activity score, *HAQ* health assessment questionnaire, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *SHS* Sharp-van der Heijde score, *VAS* visual analogue scale, measured in mm

Adjusted for age, gender and, with the exception of "IFX delayed", treatment timing

Table 3: independent predictors of increase of DAS >2.4 with restart of IFX (multivariable model)

	Hazard rate (95% CI)	Hazard rate (95% CI) after adjustment*
Shared epitope +	3.5 (1.2;10.1)	3.7 (1.3;10.6)
Smoking +	2.4 (1.3;4.6)	2.1 (1.1;4.2)
Treatment duration ≥ 18 months	2.8 (1.3;6.1)	2.4 (1.1;5.4)
Delayed treatment IFX	n.a.	1.8 (0.9;3.7)

* Model including treatment timing

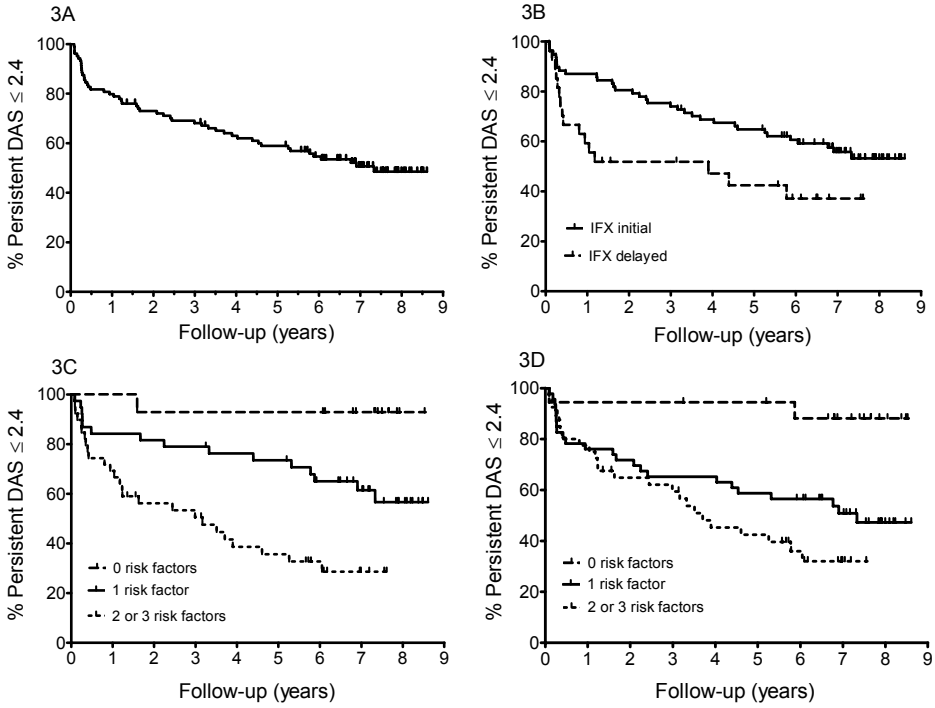

Figure 3: Kaplan Meier plots, showing the percentage of patients with persistent DAS ≤2.4 after discontinuation of IFX over time for all patients (3a), per treatment group (3b) and per number of risk factors with SE (3c) and with ACPA instead of SE (3d)

DISCUSSION

In the Best study, 45% of patients treated with infliximab could discontinue IFX. Eighty percent of these patients could stop for at least 1 year, 52% did not restart during a median follow-up of 7.2 years. In the year after IFX discontinuation, significant joint damage progression was rare, regardless of disease flare. Retreatment with IFX was successful in 84%. Smoking, SE and long IFX treatment duration (≥18 months) were independent predictors for reintroduction of IFX.

Our results are in line with previous reports, although there are differences in patient characteristics, requirements to discontinue or restart TNF-blockers, and duration of follow-up. Quinn *et al.*[7] were the first to report on successful discontinuation of a TNF-blocker (IFX), in 7/10 patients with early RA, regardless of disease activity (which in general was low). Brocq *et al.*[3] reported on 21 patients with advanced RA who were in remission after delayed treatment with a TNF-blocker (6 as monotherapy). Five patients successfully stopped the TNF-blocker for 12 months. The 16 who flared regained remission after retreatment. Saleem *et al.*[6] reported a 40% overall success rate in 2 years in 47 patients who had achieved remission and discontinued TNF-blockers. Remission was maintained in 60% of patients who had the TNF-blocker as initial treatment, compared to 3/20 patients who had had delayed treatment (10 had failed on a previous TNF-blocker). The RRR study by Tanaka *et al.*[4] has a comparable sample size to ours, and IFX was also discontinued if a DAS ≤2.4 was repeatedly achieved. The rate of successful discontinuation of IFX in 1 year was 55%, compared to 80% in 1 year in the BeSt study. This may be due to a high percentage of BeSt patients who had received IFX as initial treatment, whereas in the RRR study, all patients received IFX after failure on various systemic DMARDs. The differences in patient characteristics and follow-up duration may also explain why Tanaka *et al.* found remission at discontinuation to be predictive of maintaining a DAS ≤2.4, whereas we did not.

The percentage of infusion reactions after retreatment was not increased when compared to infusion reactions during initial treatment in group 4 of the BeSt study, so the hypothesis of Takeuchi *et al.*[8] of an increased risk of infusion reactions after reintroduction of IFX was not confirmed. This might be explained by the design of the BeSt protocol: MTX is continued after discontinuation of IFX until sustained remission is achieved on maintenance dose, and in patients in drug-free remission who flare, first methotrexate is reintroduced and increased, before IFX can be restarted. The presence of antibodies to infliximab was not tested.

The rate of serious infections was higher after reintroduction of IFX compared to during the initial treatment-period or the period of IFX-discontinuation. The difference between infection rates during discontinuation and after retreatment may be the result of physicians choosing intravenous over oral antibiotics in patients using a TNF-blocker, longer exposure to IFX or of longer and more active disease duration. The difference in serious infections between first time IFX users and restarters could reflect patient selection, since restarters had longer symptom duration and possibly more severe RA, which is associated with a higher infection risk.[12,13]

To our knowledge, the inverse association between smoking and SE and successful IFX discontinuation has not been previously reported. Both characteristics are associated with more severe disease.[14,15] Smoking, but not SE, might be associated with poor response to TNF-blockers.[15-18] Smoking and SE are associated with increased ACPA levels,[19]

but neither our analysis nor the analysis by Saleem *et al.*[6] showed a strong association between ACPA and successful discontinuation, although this may be due to relatively small numbers. For daily practice this is disappointing, since it is not current routine to test for SE. Our analyses did show that of the non-smoking, ACPA-negative patients with short IFX treatment duration, only 11% needed to restart IFX.

In the BeSt study, tapering and discontinuation of IFX was DAS steered. Therefore, the association between shorter IFX treatment duration and continued DAS ≤2.4 after discontinuation correlated with time to achieve a DAS ≤2.4 for 6 months consecutively while on IFX.

Previously, we reported that patients from the BeSt-study who received infliximab as initial treatment were more likely to achieve a DAS ≤2.4 and discontinue IFX than patients from the delayed treatment group.[20] In the current analysis, an association was found between successful discontinuation and initial treatment. Since patients in groups 1-3 only started MTX+IFX after failing on 3 treatment steps, they had longer symptom duration at time of IFX discontinuation, and probably more difficult to treat RA than the unselected patients who started with initial MTX+IFX. The differences in disease characteristics at baseline between the initial and delayed treatment groups corroborate this.(*table 1*) Despite these differences we combined patients from both groups for the analysis, because we set out to find predictors of successful discontinuation irrespective of treatment timing, and to gain power. In separate analyses for the 2 groups, we found similar effect sizes, with the exception of smoking in the delayed treatment group, possibly due to small numbers and a higher proportion of smokers in this group. Previously, we compared the response to IFX in both treatment groups using propensity scores to adjust for the differences at baseline. Since the current subanalysis compares selected patients from the 2 treatment groups who discontinued IFX because of sustained DAS ≤2.4, this method cannot be applied. The association between treatment timing and successful discontinuation was also described by Saleem *et al*.,[6] but this study had comparable limitations. Thus, the observed association is affected by patient selection based on earlier failure on at least 3 non-biological DMARD treatment steps and initiation of infliximab after a 'delay' of on average 14 months. Of course in daily practice, where TNF-blockers are currently reserved for patients who fail on non-biological DMARD, one must assume that similar selection processes are at work.

A second limitation of this subanalysis is that for 16/104 patients, SE status was not known. We included SE in the multivariable model because of the strong association with successful discontinuation. This resulted in exclusion of the patients with missing SE data.

In conclusion, infliximab can be successfully stopped for at least 1 year in 80% of patients. Joint damage does not increase in this year, regardless of flare. After a median period of 7.2 years, 52% had not restarted IFX. Even temporary discontinuation can benefit both

the individual patient and, given the high costs of TNF-blockers, society as a whole. Non-smoking, SE- or ACPA-negative patients who needed less than 18 months of IFX treatment, very rarely have to restart IFX due to an increase of the DAS to >2.4. However, not all of those who have to restart infliximab regain a DAS ≤2.4, and restarting IFX carries a (small) risk of (mild) infusion reactions. We therefore recommend that in particular for patients with one or more of the above mentioned risk factors, IFX discontinuation has to be carefully considered on an individual basis.

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Chapter 8

Do we need guidelines to stop as well as to start biological therapies for RA?

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ABSTRACT

After achieving low disease activity or remission, biological therapy might be stopped in rheumatoid arthritis patients, but information on whether and how this should be done is scarce. Successful discontinuation was highly variable since it was described in 0-97% of patients, in studies with different patient populations and follow-up durations between 12 weeks and over 7 years. In most studies, patients were required to have low disease activity or be in clinical remission for at least 6 months before biological therapy was discontinued. Significant joint damage progression in the first year after discontinuation was rare and functional ability was relatively stable in almost all patients in this year. In patients who had a disease flare, retreatment with biological therapy was successful in 70-100%. Mild infusion reactions after retreatment were described in a small number of patients. In conclusion, in the absence of a guideline for stopping biologicals in RA, we present a preliminary proposal that biological therapy can be stopped in many RA-patients after achieving low disease activity or remission for at least 6 months. Adequate monitoring of disease activity is essential, and retreatment appears to be safe and successful in many patients. Future research may further identify when and/or which patients are most likely to discontinue biological treatment successfully.

INTRODUCTION

Achieving low disease activity or remission in order to maintain functional ability and prevent joint damage is the treatment goal of rheumatoid arthritis.[1] There is evidence that treatment with methotrexate in combination with a biological agent results in more remission than treatment with methotrexate monotherapy.[2] On the other hand, biological therapies increase the risk of infections, have the potential downside of parenteral administration and have a high cost. If they are not essential to maintain suppression of rheumatoid inflammation, it would be beneficial if such therapies could be discontinued once the initial treatment goal has been achieved. There are guidelines on how to start and adjust biological therapy,[1,3] but information on if and how biological therapies can be stopped is scarce.

Can biologicals be stopped?

In addition to some case studies of biological discontinuation at the conclusion of a clinical trial[4,5], several clinical trials have included discontinuation of biologicals and subsequent follow up in their design. Patients who had a good response to biological treatment, by various definitions, were eligible for biological discontinuation.(*table 1*)

Consequences of discontinuation

All 17 patients who had to discontinue infliximab at the end of the ATTRACT trial, and all 4 patients who had to discontinue tocilizumab at the end of the SAMURAI trial, flared.[4,5] Discontinuation of TNF-inhibitors resulted in disease flare in between 22% and 71% of patients in 3 other small trials.[6-8] In the BeSt study and the RRR study, just over 50% of patients had a disease flare after discontinuation of infliximab.[9-11] Discontinuation of adalimumab as part of the HONOR and OPTIMA study was followed by loss of clinical remission (HONOR) or low disease activity (OPTIMA) in 43% and 19%, respectively.[12,13] In the HIT HARD study, adalimumab was stopped in all patients after 24 weeks; 44% were still in remission after 24 weeks of follow-up, compared to 47% at discontinuation.[14] Subcutaneous abatacept was discontinued after DAS improvement >0.6 in the ALLOW study, followed by a disease flare in 3% in the next 3 months.[15] In all cases of biological discontinuation, co-medication with methotrexate or other disease modifying antirheumatic drugs was initially continued.(table 1)

Biological therapy is very effective in suppressing joint damage, possibly even when there are still symptoms of inflammation.[16] Brocq *et al.* showed that 4/5 of the patients who did not show a relapse also showed no radiological progression, while one patient showed erosion progression only in 1 joint.[6] In the RRR study, no progression was seen in 22/33 relapse-free patients and in 7/16 who did have a relapse.[9] On a group level there was no significant progression in either group: they had a median change in Sharp-van

der Heijde score (SHS) of 0.0 and 1.5 respectively a year after discontinuation. In the BeSt study, median damage progression in the year after discontinuation was 0 as well.[10] Damage progression >5 point SHS occurred in 4 patients, one of whom had relapsed and restarted infliximab in that year. In the HONOR study, mean damage progression (SHS) 1 year after discontinuation was -0.2 in the 10 patients with radiological data who were still in remission, and 1.9 in the 7 patients who flared.[13]

From a patient point of view, minimal radiological damage progression is irrelevant if it does not influence functional ability. None of the 9 patients in Quinn's study who discontinued infliximab showed detoriation of functional ability.[7] In the RRR study, the median Health Assessment Questionnaire (HAQ) score was 0.2 in the relapse-free group and 0.6 in the relapse group.[9] In the BeSt study, no difference in functional ability was seen 1 and 3 years after discontinuation of infliximab, irrespective of whether biological therapy had to be restarted. However, after 5 years, patients who had restarted infliximab did show a slight deterioration of functional ability: HAQ score changed from 0.3 to 0.7.[10] In the OPTIMA study, the mean HAQ score a year after discontinuation was not different from the HAQ in the group that had continued adalimumab.[12] The patients form the HIT HARD study showed a rise in mean HAQ of 0.11 points 24 weeks after discontinuation.[14]

Retreatment

Reintroduction of biological therapy was successful in 85-100% of the patients of the ATTRACT study, BeSt study, the study by Brocq *et al*. and the patients who restarted tocilizumab after the SAMURAI study.[4-6,10] In the RRR study, retreatment was effective in 32/46 (70%) patients.[9] No adverse events or infusion/injection site reactions were described in the ATTRACT study, the ALLOW study or the studies by Brocq *et al*. Mild infusion reactions occurred in 2/4 retreated patients (who had a history of drug hypersensitivity) in the SAMURAI study, 5/50 retreated patients in the BeSt study and in 5/46 patients in the RRR study.[5,9,10] In the BeSt study, this was compared to the number of infusion reactions in patients first treated with infliximab and no significant differences were found, indicating that retreatment did not seem to increase the risk of infusion reactions. The ALLOW study was the only study in which antibodies to the biological therapy were measured. They were found in 7/73 patients who had discontinued abatacept for 3 months, compared to none of the 38 patients who had continued abatacept. Response to therapy did not seem to be influenced by these antibodies, as disease activity 12 weeks after reintroduction of abatacept was similar to disease activity in the group with continued treatment.

Discontinuation strategies

In the 2010 EULAR recommendations it is stated that it is currently unclear how to discontinue treatment in patients who have achieved remission.[1] It is advised to consider slow tapering of biological therapy only in patients who have been in 'persistent remission' and

only after glucocorticoids have been tapered first. According to expert opinion, persistent remission should be defined as remission for at least 12 months. There are few studies that include systematical long term follow up of patients who achieve clinical remission.
As described in table 1, most studies have discontinued biological treatment at higher levels of disease activity and earlier. It may be that fewer patients would relapse if long term remission was maintained before discontinuation. On the other hand, if strategies are in place to detect an increase in disease activity early and restart treatment immediately, it may be acceptable to aim at a temporary drug holiday rather than permanent drug free remission. To spare patients the most severe flares, it would help to be able to identify which patients are likely to discontinue biologicals successfully.

Predictors of successful discontinuation

The reported predictors of successful discontinuation differ per study. Saleem *et al.* found shorter disease duration, better functional ability at discontinuation and shorter symptom duration before starting any treatment to be predictive of successful discontinuation. Brocq *et al*. found that patients who were male, rheumatoid factor negative, had longer biological treatment duration, and/or a longer mean time in remission less often had to restart biological therapy. The RRR study and the HONOR study found that patients who had a low DAS28 (≤2.2 and ≤1.9 respectively) at discontinuation were least likely to have to restart treatment. In the HONOR study, patients with a low HAQ before starting treatment had to restart less often. In the BeSt study, rapid achievement of low disease activity on infliximab, non-smoking and absence of HLA shared epitope were independent predictors of successful discontinuation. There is a suggestion that initial treatment with biologicals results in more successful discontinuation than delayed treatment, but this may at least in part be explained by selection bias.

Do we need discontinuation guidelines?

From these studies we can conclude that in patients who have been in prolonged (at least 6 months) low disease activity or remission, discontinuation of biological therapies is an appropriate option. In the short term, this will have no consequences for radiological damage progression or functional ability in the majority of patients.[6,8-10] If disease activity increases and patients need retreatment, this seems to be safe and effective, although in the RRR study and in long term follow-up in the BeSt study, some patients who had to be retreated had a small increase in HAQ score.
Outside of clinical trials, reports of discontinuation of biological agents other than because of side effects, contraindications or failure to respond are scarce. Recently, van der Maas *et al*. described an observational cohort in which down-titration of infliximab in patients with a DAS28 <3.2 led to infliximab-free low disease activity in 8/51 patients.[17] No follow-up of these patients was described.

There may a discrepancy between findings in clinical trials and experience in daily practice. The patient populations may differ, as well as patients' and physicians' expectations about treatment (dis)continuation. Most patients on biologicals outside clinical trials have started those treatments only after prolonged high disease activity and failure on other drugs. One can understand that they would be anxious not to risk a relapse. On the other hand, serious complications during treatment with biologicals may occur in some patients, and unnecessary continuation of such drugs therefore is unwise.
In some countries, patients must pay for part or all of the medication costs themselves. Although this may cause delays in treatment initiation, it also results in more patients willing to discontinue when it appears safe.

The clinical trials have shown that for some patients at least, rheumatoid arthritis is not so much a chronic disease that needs constant suppression with immunomodulating drugs, but rather a disease that requires a strategy of induction and consolidation therapy, followed by tapering and discontinuation of medication. It is obvious that relapses can happen, and we need monitoring strategies with scoring of disease activity to ensure that rapid, and perhaps again temporary, treatment is restarted. Future research should focus on identifying patients most at risk for relapsing who need the most intensive monitoring, optimizing the monitoring strategy itself (frequency, possible contributions of imaging techniques and biomarkers if the usual composite scores are insufficient or impractical), and on optimizing the induction and consolidation therapies (timing, choice of drugs, treatment target, continuation of co-medication). In addition to longer follow-up data from clinical trials, daily practice based observational studies with sufficiently long and systematic follow up are also needed. Patients' expectations and wishes should be incorporated in such research. Administrators will require real time cost-utility analyses.

In conclusion, it seems too early to provide detailed guidelines for discontinuation of biologicals, but we would like to propose three recommendations. Recommendation 1: if patients have had low disease activity or been in remission for at least 6 months, consider trying it! Discontinuation of biological therapy has been shown to be possible for at least 1 year in 29-80% of patients who had had low disease activity or been in remission for at least 6 months. Recommendation 2: once biologicals are discontinued, as ever, keep monitoring disease activity, functional ability and radiological damage progression. During the year following biological discontinuation, radiological damage progression was rare and functional ability was maintained in the majority of patients. But a deterioration in either of those would suggest to follow up with recommendation 3: restart treatment as soon as it appears that the disease is relapsing. Retreatment was effective in 70-100% of patients. Infusion reactions after retreatment with infliximab were mild and in a low frequency comparable to that observed during initial infliximab treatment. We look forward to reports on such projects.

Table 1: overview of a number of studies on discontinuation of biological therapy in rheumatoid arthritis patients

	Patients	Treatment	Withdrawal	Follow-up	Biological-free period	Results	Predictors of relapse	Result of retreatment
ATTRACT 2004[4]	1987 RA, active disease despite methotrexate, n=17 (all trial patients from Leeds who entered the extension phase)	Infliximab 3 or 10 mg/kg per 4 or 8 weeks+ methotrexate (corticosteroid allowed)	In all patients at t=24 months	9 months	Methotrexate (corticosteroid allowed)	DAS: 17/17 flared within 15 weeks HAQ: no data Radiology: no data	No data	15/17 retreated: no infusion reactions or toxicity, 12/15 good ACR respone, 2 not, 1 stop (pregnancy wish)
Quinn 2005[7]	Early RA (<1yr), no previous DMARD or corticosteroid, n=10	Infliximab 3 mg/kg+ methotrexate, 1 pt only 1 infusion of infliximab	In all patients at t=54 weeks (last dose t=46 weeks) (9 had good response, 1 did not)	1 year	Treatment according to rheumatologist's preference	DAS: 2/9 flared ≥32 weeks after last infusion: increase in DAS28 HAQ: no detoriation of functional ability Radiology: no data	No data	No retreatment

Table 1: overview of a number of studies on discontinuation of biological therapy in rheumatoid arthritis patients (*continued*)

	Patients	Treatment	Withdrawal	Follow-up	Biological-free period	Results	Predictors of relapse	Result of retreatment
Brocq 2009[6]	1987 RA patients using anti-TNF, not a history of relapsing after discontinuation of anti-TNF, n=21	Infliximab (n=2) 3mg/kg, etanercept 50 mg/week (n=7)/25mg/week (n=7) or adalimumab 40 mg/2 weeks (n=4)/40mg/3 weeks (n=1), stable DMARD and corticosteroid dose (≤5mg) for 6 months	If DAS28 <2.6 for ≥6 months and biological on maintenance dose or lower,	1 year	DMARD (and corticosteroid) on a stable dose, 5 drug-free	DAS: 15/21 flared, 1 died, of the 5 relapse free, 2 were drug-free, of the 4/15 who relapsed had been drug-free HAQ: no data Radiology: in relapse free patients: 4 no progression, 1 progression of a pre-existing erosion	Shorter treatment duration with anti-TNF, shorter mean time in remission, male gender, RF negativity	13/15 remission within 2 months, 2/15 remission after 4 and 5 months: 100% again remission No adverse events
RRR 2010[9]	RA 1987, not achieving LDA on methotrexate 3 months n=114	Infliximab 3mg/kg (possibly in some patients with methotrexate, unclear)	If DAS28 <3.2 for 24 weeks, concomitant methotrexate started,	1 year	Methotrexate, <5 mg prednisolone, prednisolone could be tapered	DAS: 46/102 flared (DAS28 ≥3.2), 12 withdrew HAQ: 0.2 for relapse-free, 0.6 for relapse Radiology: data from 49/114: 22/33 relapse free and 7/16 with relapse deltaSHS<0.5, median progression 0.0 vs 1.5	High (>2.2) DAS28 at cessation	32/46 effective retreatment. Minimal infusion reaction in 5/46

Table 1: overview of a number of studies on discontinuation of biological therapy in rheumatoid arthritis patients (*continued*)

	Patients	Treatment	Withdrawal	Follow-up	Biological-free period	Results	Predictors of relapse	Result of retreatment
Saleem 2010[8]	1987 RA n=47	TNF-blocker + methotrexate: 27 initial combination therapy, 10 failed ≥ 2 DMARD, 10 failed ≥ 2 DMARD and a TNF-blocker	If DAS28 <2.6 on stable therapy for ≥6 months,	1 year	Methotrexate	DAS: 28/47 flared (DAS28≥2.6) HAQ: no data Radiology: no data	Longer disease duration, higher HAQ at cessation, higher RAQoL at cessation, longer symptom duration before starting any treatment, delayed treatment? Multivariate, in initial treatment group: symptom duration at start of first treatment, high inflammation related cell frequency, high regulatory T cell frequency, low proportion of naïve T-cells	No data
ALLOW 2011[15]	1987 RA, high disease activity, using methotrexate for 3 months prior to study period, 10% had used previous biological, n=80	Abatacept + methotrexate 12 weeks	In all patients with ΔDAS28 ≥6 after 12 weeks, retreatment after 12 weeks or if flare,	12 weeks	Methotrexate stable dose + placebo + in 55% low dose prednisolone (<10 mg), 1 patient high dose	DAS: mean DAS28 increase 0.39, 2/80 flared before end of 12-week period because of lack of efficacy HAQ: no data Radiology: no data	No data	7/73 antibodies vs 0/38 in continued abatacept group No injection site reactions or other injection related AE's

Table 1: overview of a number of studies on discontinuation of biological therapy in rheumatoid arthritis patients (*continued*)

	Patients	Treatment	Withdrawal	Follow-up	Biological-free period	Results	Predictors of relapse	Result of retreatment
BeSt 2011[10]	1987 active RA, n=104	Initial (n=77) and delayed (n=27) infliximab with dose escalation when needed plus methotrexate	DAS44≤2.4 for ≥6 months on infliximab 3mg/kg, mean	7.2 years	Methotrexate monotherapy, dose escalation when needed, tapering when continued remission	DAS: 50/104 flared HAQ: 5 years after cessation: HAQ 0.7 versus 0.3 at cessation in restarters, patients who did not flare continued to have a HAQ of 0.1 Radiology: Median damage progression 0 in year after cessation, 4 patients progression>5 (1 flared)	Smoking, long time to achieve low disease activity on treatment, presence of HLA shared epitope, delayed treatment?	42/50 good response, 2/50 not (yet), 6 patients stop, 5/50 mild infusion reaction
HIT HARD 2011[14]	Active RA n=87	Adalimumab 40mg/2 weeks plus methotrexate s.c. 15mg/week	Withdrawal after 24 weeks in all patients,	24 weeks	Methotrexate monotherapy s.c. 15mg/week	DAS: mean DAS28 increase 0.2 points, 47% had remission, 3% lost remission HAQ: mean HAQ increase 0.11 points Radiology: no specific data	No data	No data

Table 1: overview of a number of studies on discontinuation of biological therapy in rheumatoid arthritis patients (*continued*)

	Patients	Treatment	Withdrawal	Follow-up	Biological-free period	Results	Predictors of relapse	Result of retreatment
OPTIMA 201t1[13]	Active RA, n=102	Adalimumab plus methotrexate for 26 weeks	Stable low disease activity (DAS28),	52 weeks	Methotrexate plus placebo	DAS: 19% lost low disease activity HAQ: mean HAQ 52 weeks after discontinuation 0.35 Radiology: no specific data	High HAQ at baseline	No data
HONOR 2011[12]	Active RA, n=30	Adalimumab plus methotrexate, ≤5 mg steroids per day	Das28< 2.6 for >24 weeks,	6 months	Methotrexate	DAS: 43% lost remission, 27% high disease activity HAQ: no data Radiology: at t=1 year in 17 patients: change in mean SHS -0.2 for patients in continued remission, 1.9 for patients who flared (n=7)	DAS28 >1.9 at discontinuation	No data

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Chapter 9

Drug-free remission, is it already possible?

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ABSTRACT

Purpose of review To give an overview of recently published articles covering drug-free remission in rheumatoid arthritis.

Recent findings Recent studies covering drug-free remission showed differences in numbers studied, remission definition, disease duration and medication used. Drug-free remission was reported in 9-29%. Only 2/4 studies reported on patients who restarted medication due to a disease flare or loss of remission, which occurred in 45-46%. In the BeSt study, remission or low disease activity was achieved again after retreatment within 6 months in 96%. In the Finnish ERA study, none of the patients achieved remission after retreatment, their mean DAS28 was 3.68. Joint damage progression was not higher in patients who restarted medication when compared to patients in sustained drug-free remission or patients with continued treatment. ACPA, RF or SE negativity and short symptom duration were independent predictors of successful drug-free remission in more than 1 cohort.

Summary Drug-free remission can be achieved and sustained in a small group of RA patients. In early RA, retreatment is successful in the majority of patients. Disease flare after cessation of medication does not seem to increase joint damage progression. Sustained drug-free remission is predicted by auto-antibody and SE negativity and short disease duration before treatment initiation.

INTRODUCTION

Remission is the current treatment goal in rheumatoid arthritis.[1] Increasing numbers of patients in clinical trials achieve this goal.[2] This raises the question whether patients who have been in remission for a prolonged period still need medication. Although old studies have observed different remission rates in population-based RA and hospital based RA,[3] the current review has focused on hospital-based RA. Several small studies conducted in the 1970's and '80's show high relapse rates after cessation of Disease Modifying Anti-Rheumatic Drugs (DMARD),[4-8] with the exception of one trial in patients treated with high doses of gold.[9] In 1996, ten Wolde *et al.* published a double-blind placebo controlled study on 285 patients with longstanding RA in remission, who were randomized to continuing their DMARD, or to switch to placebo.[10] The sustained drug-free rate was 62% in 1 year in the drug-free (placebo) group. The BeSt study was the first large treatment strategy trial to show that in 65% of patients in remission, medication could be stopped without losing remission during median 11 months.[11] In this review, we discuss the most recent trials covering drug-free remission, radiological damage progression in drug-free patients, response after retreatment, and predictors of sustained drug-free remission.

Recent trials investigating drug-free remission

Predictors of sustained drug-free remission were studied[12] in the Leiden Early Arthritis Clinic (EAC) and the British Early Rheumatoid Arthritis Study (ERAS).(*table 1*) The follow-up duration of patients from these cohorts varied, with a maximum of 10 years. For the purpose of this study, drug-free remission in de EAC and ERAS was defined as having no swollen joints and drug-free remission according to the treating rheumatologist. The 454 patients from the Leiden EAC had RA according to the 1987 American Rheumatism Association (ARA, now ACR) diagnostic criteria at, or within one year after diagnosis. They were included between 1993 and 2002, and their mean symptom duration at inclusion was 6.4 months. Patients were either treated with analgesics, followed by hydroxychloroquine (HCQ) or sulfasalazine (SSA) in case of an insufficient response, or with initial HCQ, SSA or methotrexate (MTX), depending on their inclusion period. Sustained drug-free remission, defined as drug-free remission for at least 1 year consecutively, was achieved in 68/454 patients (15%). The 895 patients from the ERAS with recent onset RA according to the 1987 ARA criteria, were diagnosed slightly earlier, between 1986 and 1996. Their mean symptom duration at inclusion was 8.3 months. Patients were treated according to their rheumatologist's preference. Most patients were first treated with analgesics, followed by sequential monotherapy or combination therapy with synthetic DMARD in severe RA, in case of an insufficient response. Drug-free remission during at least 1 year was achieved in 84/895 patients (9.4%).

Table 1: studies covering drug-free remission published between June 2009 and December 2010

Reference (trial)	n follow-up complete	Inclusion*	Follow-up	Treatment	Cessation criteria	Retreatment criteria	n drug-free (%)	n sustained drug-free
Van der Woude et al (Leiden EAC)[12]	454/590	- Mean symptom duration 6.4 months - RA according to 1987 criteria at, or within 1 year after inclusion	Max 10 years	Analgesics, followed by synthetic DMARDs, or initial synthetic DMARD monotherapy	No swollen joints, remission according to rheumatologist	Retreatment not reported, sustained defined as ≥ 1 year		68/454 (15%)
Van der Woude et al (ERAS)[12]	895/1279	Mean symptom duration 8.3 months	Max 10 years	Analgesics, followed by sequential monotherapy or combination therapy in case of more severe RA, with synthetic DMARDs	No swollen joints, remission according to rheumatologist	Retreatment not reported, sustained defined as ≥ 1 year		84/895 (9%)
Tiipana-Kinnunen et al (Finnish ERA)[13]	70/87	Mean symptom duration 8 months	15 years	Sawtooth strategy with synthetic DMARDS, 4% treated with biologicals. Intramuscular glucocorticoids im and oral during active disease	1981 ACR remission criteria (14) excluding fatigue for ≥1year/ prolonged symptom free phase with minor disease activity	Disease flare	20/70 (29%)	11/70 (16%), of which 64% in remission at t=15 years
Hetland et al (CIMESTRA)[15]	139/160	- Median symptom duration 3.2 months in MTX+CSA group, 3.9 months in MTX+ placebo group - ≥2 swollen joints	5 years	Dynamic protocol: initial DMARD combination therapy vs initial monotherapy+placebo, + intraarticular glucocorticoids, see text	1981 ACR remission criteria ≥ 1 year	Retreatment not reported	17%	
Klarenbeek et al (BeSt)[16]	508 intention to treat analysis	Median symptom duration 23 weeks (≈ 5.8 months) - ≥ 6 swollen, ≥ 6 tender joints	5 years	Dynamic protocol aimed at DAS ≤2.4: Monotherapy or combination therapy with synthetic DMARDs, prednisolone, biologicals see text	DAS <1.6 for ≥ 6 months	Increase of DAS to ≥1.6	115/508 (23%)	59/508 (12%)

*Only patients with RA according to 1987 ARA criteria at diagnosis were included, unless stated otherwise

DMARD Disease Modifying Anti-Rheumatic Drug, ACR American College of Rheumatology DAS Disease activity score (53 tender, 44 swollen joints)

Drug-free remission and retreatment were studied in 70 Finnish early rheumatoid arthritis (ERA) patients,[13] in a prospective cohort study started in 1986 with a follow-up of 15 years. Median disease duration at inclusion was 8 months. Patients were treated according to the 'sawtooth treatment strategy'.

Most patients used conventional DMARD monotherapy and combination therapy in case of insufficient response, 4% used biologicals. DMARD were discontinued if remission according to the 1981 American College of Rheumatology (ACR) criteria[14] was achieved for at least 1 year, or in case of a prolonged symptom-free phase with minor disease activity. Nine (45%) out of the 20 patients who had been drug-free restarted treatment after a disease flare, after a median duration of 50 months. Of the 11 patients who had not restarted medication, 64% were in remission, the other 36% had low disease activity.

In the 5-year follow-up of the double-blind CIMESTRA trial, Hetland *et al*.[15] reported on the drug-free remission rate of 139 recent onset RA patients, included between 1999 and 2002. Patients were treated according to a dynamic treatment protocol. Initially, patients were randomized to receive either MTX+ciclosporin (CSA) or MTX+placebo. Both group received 2-weekly, and then monthly intraarticular bethamethasone injections in the first 52 weeks. HCQ was added after 68 weeks. After 2 years, MTX+CSA+HCQ triple therapy and then biologicals were started in case of insufficient response. The mean symptom duration at inclusion was 3.2 months in the combination therapy group and 3.9 months in the MTX+placebo group. After achieving remission according to the 1981 ACR criteria for at least 1 year, DMARDs were tapered and finally stopped. Drug-free remission at year 5 was achieved in 17% with no differences between the 2 initial treatment groups: 14% in the MTX+placebo group and 19% in the combination therapy group (p-value 0.68).

The most recent study on drug-free remission is the 5-year analysis of the 508 recent-onset RA patients from the double-blind BeSt trial, who were included between 2000 and 2002.[16] Median symptom duration at inclusion was 23 weeks (5.8 months). Patients were randomized in 4 treatment groups: sequential monotherapy, step-up combination therapy, initial combination therapy with prednisolone or initial combination therapy with a TNF- blocker (infliximab). Treatment was adjusted every three months in case of an insufficient response, differently for each treatment group. In group 1-3, combination therapy with a TNF-blocker was started after patients had failed on 3 previous treatment steps with synthetic DMARD including at some time prednisolone in groups 2 and 3. After a DAS (53/44 joint count) <1.6 on monotherapy was achieved for at least 6 months, medication was stopped. Drug-free remission was achieved in 115/508 patients (23%), with no significant differences between the four treatment groups. In 46%, DMARD had to be restarted due to a rise in disease activity to a DAS ≥1.6. The 51% in sustained drug-free remission had a median follow-up of 23 months after cessation of DMARD.

Response after retreatment

Clinical and radiological response in restarters was studied in two of the trials.(*table 2*) In the Finnish ERA study,[13] restarters had a significantly higher mean DAS28 at t=15 years than patients in sustained drug-free remission: 3.68 (SD 1.23) versus 2.08 (SD 1.01), with a p-value of 0.0018. The mean DAS28 in continued DMARD users was also slightly lower: 3.37 (SD 1.01). The mean scores on the Health Assessment Questionnaire (HAQ) of the three groups were not significantly different. Radiological damage after 15 years in restarters was also comparable to the other 2 groups. Restarters had a mean Larsen score of 25 (SD 30). There was a significant difference between continued DMARD users and patients in sustained drug-free remission. Their mean Larsen scores were 54 (SD 36) and 12 (SD 18), respectively, p<0.001.

In the BeSt study,[16] retreatment was successful in 96%: 25/53 patients achieved remission again within 3 months, 14/53 patients within 6 months, 11/53 achieved low disease activity. Two patients (4%) were lost to follow-up, 1 patient did not achieve low disease activity. The median HAQ scores of patients in drug-free remission and restarters were comparable to the scores of the general population. Significant radiological damage progression was not seen in the majority of drug-free patients in the first year after discontinuation of DMARD. Radiological damage progression in the first year of increase of disease activity in patients who needed retreatment was not different when compared to radiological damage progression in the first year after discontinuation of medication in patients in sustained drug-free remission. Median Sharp progression scores were 0 (IQR 0-1) and 0 (IQR 0-0) respectively, p-value 0.44.

Predictors

Although cessation of medication appears to be relatively safe with in general good response after retreatment and no increase in radiological damage progression, some patients don't achieve remission again after retreatment. Therefore, predictors of sustained drug-free remission are needed.

Van der Woude *et al*.[12] studied independent predictors of sustained drug-free remission, defined as drug-free remission for at least 1 year consecutively, in the Leiden EAC cohort and tried to replicate these results in the British ERAS cohort. The strongest predictor for sustained drug-free remission in the Leiden EAC cohort was anti-citrullinated protein antibody (ACPA) negativity, but ACPA status was not known for patients from the ERAS cohort. Rheumatoid factor (RF) negativity, Shared epitope (SE) negativity and short symptom duration at baseline were found to be independent predictors in both cohorts.(*table 2*)

A separate analysis of predictors of sustained drug-free remission was not described by Tiippana-Kinnunen *et al*.[13] in their Finnish ERA study. They did find an association with RF negativity and non-erosiveness at baseline and sustained drug-free remission.

Table 2: response after retreatment and predictors of sustained drug-free remission

Reference (trial)	Disease activity after retreatment	Radiographic damage	Predictors of sustained drug-free remission
Van der Woude (Leiden EAC and ERAS)	Not reported	Not reported	**Univariable**: RF, SE negativity, ACPA negativity in EAC, acute onset of symptoms, baseline low disease activity and low HAQ in ERAS **Independent predictors**: short symptom duration, low baseline CRP and ACPA negativity, or short symptom duration, RF negativity and SE negativity
Tiippana-Kinnunen (Finnish ERA)	Mean DAS28 at t=15 years 3.68 (SD 1.23), 0% remission, mean HAQ 0.38 (SD 0.51)	Mean Larsen scores at t=15 years: Continuous treatment group: 54 (36) Restarters: 25 (30) Successful drug-free group: 12 (18), p<0.001	Association with RF negativity, non-erosiveness
Klarenbeek (BeSt)	96% good response: 47% again clinical remission within 3 months, plus 26% after 6 months, 21% again low disease activity, median HAQ 0.20 (IQR 0.15-0.34)	Median increase in Sharp van der Heijde scores after 1 year drug-free: Restarters 0 (IQR 0-1) Sustained drug-free: 0 (IQR 0-0) p=0.44	**Univariable**: ACPA/RF negativity, higher HAQ at baseline, higher VAS global health at baseline **Independent predictors**: ACPA negativity, lower disease activity until remission, higher baseline HAQ, MTX compared to SSA as last DMARD before drug-free remission

ACPA Anti citrullinated protein antibodies *RF* Rheumatoid factor *SE* Shared epitope *DAS* Disease Activity Score *HAQ* Health Assessment Questionnaire *VAS* Visual analogue scale *SSA* Sulfasalazine *MTX* Methotrexate *DMARD* Disease Modifying Anti-Rheumatic Drug

ACPA negativity was also found to be the strongest predictor of sustained remission in the BeSt study,[16] followed by low DAS until remission, a higher baseline HAQ and SSA as last DMARD when compared to MTX. RF negativity was associated with sustained drug-free remission in the univariable analyses.

In summary, all trials found RF negativity to be associated with sustained drug-free remission. ACPA negativity was found to be an even stronger predictor in those cohorts that measured ACPA status. Short symptom duration before treatment initiation and SE negativity predicted sustained drug-free remission in two cohorts.

Translation to clinical practice and consequences for further research

The four recent studies on drug-free remission cover a heterogeneous patient population, treated according to different strategies. Different remission definitions and criteria for retreatment were used. The available sets of remission criteria vary in components used and in stringency.(*table 3*)

It is therefore hard to draw general conclusions. These recent studies and previous publications do show that drug-free remission is indeed possible in 17-29% of patients. Sustained (>1 year) remission was reported in an even smaller group: 9-16% of all patients. Retreatment was needed in 44-45% of all drug-free patients in recent studies[13,16] and in 11-100% of all drug-free patients in older publications.[4-6,17] More research on sustainable drug-free remission is necessary, with longer follow-up. Preferably, these studies would use a uniform set of remission criteria. Recently, new criteria have been proposed by the ACR/EULAR Commission to Redefine Remission in Rheumatoid Arthritis.[18] In contrast to the ACR 1981 criteria, these criteria allow for 1 swollen and 1 tender joint. This does raise the concern that patients in remission might still have active synovitis, causing joint damage.[2] Only two of the 115 patients in DAS remission (which shows similarities with the new criteria (*table 3*)) from the BeSt study, showed clinically relevant joint damage progression in the first year after cessation. Unfortunately, long-term radiologic follow-up of patients in drug-free remission is not yet available. This underlines the importance of monitoring of disease activity and joint damage progression in patients in drug-free remission. Future research should also focus on radiological joint progression in drug-free patients with longer follow-up duration. Secondly, one wonders if patients who have discontinued all anti-rheumatic drugs can taper or need to intensify other therapies such as NSAIDs or physical therapy, but none of the papers offer information on that.

Furthermore, only few studies report on the effect of retreatment: do patients respond well to therapy again? The positive results from the BeSt study, which included 508 patients, and had a dynamic treatment protocol in which treatment effect was evaluated every three months, suggest that this is indeed the case. Retreatment was successful in 96%. DMARD were stopped when patients were in DAS-remission for at least 6 months and restarted when remission was lost. These results are in line with some smaller studies conducted between 1976 and 1987 investigating cessation of and retreatment with synthetic DMARD[4,5,7] and a more recent trial which studied cessation of and retreatment with biologicals,[19] which all report a good response after retreatment in all patients. However, in the study of ten Wolde *et al*., only 78% had a good response to retreatment[20] and in the Finnish ERA trial, the majority of patients did not achieve low disease activity during follow up after retreatment. A possible explanation for these differences is that in these studies, treatment was restarted when disease flared to moderate or high disease activity, where in the BeSt study patients were retreated when an increase in DAS to >1.6 occurred. Secondly, not all patients in the Finnish trial were in clinical remission when medication was stopped. These results suggest that DMARD should only be stopped in patients in sustained clinical remission. Treatment should be restarted as soon as remission is lost, without delay.

Table 3: comparison of remission criteria

Criteria or composite index (14;17)	ACR 1981 criteria	Modified ACR criteria	FDA criteria	Preliminary new ACR remission criteria	DAS<1.6*	DAS28<2.6*	SDAI ≤3.3	CDAI ≤2.8
Total of swollen & tender joints**	0	0	0	≤1/28 swollen and ≤1/28 tender	≤1/44 swollen and ≤1/53 tender	≤1/28 swollen or ≤1/28 tender	0/28 swollen, 0/28 tender	0/28 swollen, 0/28 tender
Systemic inflammation	ESR <30 mm/h female, <20 mm/h male	ESR <30 mm/h female, <20 mm/h male	ESR <30 mm/h female, <20 mm/h male	CRP ≤1	ESR or CRP	ESR or CRP	CRP	
Other criteria	1. Duration of morning stiffness ≤15 min 2. No fatigue 3. No tenderness or pain in motion 4. No tendon sheet swelling	1. Duration of morning stiffness ≤15 min 2. Pain (VAS) ≤1cm 3. No tendon sheet swelling	1. ACR 1981 criteria 2. No DMARDs 3. Radiographic arrest (Larsen or Sharp) ≥6 months	1. Patient global assessment (VAS) ≤1 cm	1. Patient's assessment of global health (VAS)	1. Patient's assessment of global health (VAS)	1,2. Patient's and evaluator's assessment of disease activity (VAS)	1,2.Patient's and evaluator's assessment of disease activity (VAS)

ACR American College of Rheumatology, *FDA* US Food and Drug Administration, *DAS* Disease Activity Score, *SDAI* Simplified Disease Activity Index, *CDAI* Clinical Disease Activity Index, *ESR* Erythrocyte Sedimentation Rate, *CRP* C-reactive protein, *VAS* visual analogue scale

*Calculated with CRP for comparison with SDAI and CDAI. Hypothetically, for patients in DAS remission a larger number of swollen joints would be possible if these were not tender.

**For composite indices: calculated assuming CRP =1 mg/dL, VAS scores= 1cm

CONCLUSION

There are few studies that report on drug free remission in RA and even fewer that report on restart of treatment. From 4 recent studies in patients with recent onset RA with a follow-up duration up to 15 years, the following conclusions can be drawn:

- Drug-free remission is achieved in 17-29% of patients and sustained in 9-16% during 1-4 years.
- Joint damage progression in drug-free patients is not different from DMARD users and does not increase in the first year(s) of drug-free remission, regardless of flare.
- Low disease activity is achieved again in the majority of patients who have to restart treatment.
- Auto antibody negativity (RF, ACPA), shared epitope negativity and short symptom duration before treatment initiation are predictors of sustained drug-free remission.

The low rates of drug-free remission are possibly due to the fact that the treatment of these patients was aimed at achieving low disease activity, at best. With new treatment options more patients can now be treated to achieve remission, and potentially this will lead to more drug free remission in the future. Clinical research should focus on the consequences of drug-free remission and retreatment after longer-follow up and on identifying predictors of sustained drug-free remission.

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Chapter 10

Is achieving remission associated with better health related quality of life than maintaining low disease activity in rheumatoid arthritis patients?

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ABSTRACT

Objective To assess if achieving remission is associated with a better health related quality of life (HRQoL) than maintaining low disease activity (LDA).

Methods Data were used of 508 patients with recent onset rheumatoid arthritis (RA) participating in the BeSt study, whose treatment was steered at LDA (DAS≤2.4), to investigate the relationship between DAS and HRQoL. Two summary scales of the Short Form-36 were used: the Physical and Mental Component Scale (PCS, MCS). Three linear mixed models were specified with PCS/MCS as dependent variable and with disease activity category, change in DAS score or change in disease activity category as independent variables. Remission was defined as DAS<1.6, or, separately, according to the ACR/EULAR remission criteria.

Results Patients in remission (DAS<1.6) compared to LDA had a significantly better PCS and MCS, with a difference of 4.0 and 1.0 points respectively (p<0.001). An increase of 1 point in DAS was associated with a decrease of 4.6 (95% CI 4.4;4.8) in PCS and a decrease of 1.6 (95% CI 1.3;1.9) in MCS. Achieving DAS-remission resulted in a 3.8 point gain in PCS compared to maintaining LDA, but no difference in MCS. Similar results were found for remission according to the ACR/EULAR criteria.

Conclusion Improvement of disease activity is associated with improvement of HRQoL, with also a clinically relevant improvement in PCS score for patients achieving remission when compared to maintaining LDA. Patients who move from LDA to remission gain 4 points in PCS, but show no significant improvement in MCS.

INTRODUCTION

Advances in treatment for RA patients have led to improved clinical and structural outcomes. Following recent recommendations, treatment should be started early and requires adjusting the medication until a target of remission or at least low disease activity (LDA) is achieved.[1,2] Achieving such a target is associated with better functional ability and less radiological damage.[3]

It remains unclear if it would be better to treat to the target of remission than of LDA as comparative studies are lacking. Also, the influence on Health Related Quality of Life (HRQoL), of achieving these different levels of disease activity is uncertain. As HRQoL reflects a more broad perspective of the influence of disease on daily life than most outcome measures, it may give more guidance on which disease activity level should be preferred.

Therefore we investigated in a low disease activity targeted cohort including early RA patients whether 1) remission or achieving remission was associated with a better HRQoL than LDA or maintaining LDA and whether 2) a change in disease activity was associated with a relevant change in HRQoL.

METHODS

Patients

Five-year follow-up data from the BeSt trial were used, where 508 patients with recent onset active RA were dynamically treated according to a step-wise treatment protocol aiming at a disease activity score (DAS) ≤2.4. Patients were randomized to four different treatment strategies: 1. sequential monotherapy; 2. step-up combination therapy; 3. initial combination therapy with prednisolone and 4. initial combination therapy with infliximab. Clinical assessment of disease activity was performed every three months, and included a joint count for tenderness and swelling, erythrocyte sedimentation rate (ESR) and patient's assessment of global disease activity. This study was approved by the ethical committees of participating centers and all patients provided informed consent. More details about the BeSt study have been described elsewhere.[4]

Outcome assessment

HRQoL was assessed with the Short Form 36 version 2 (SF-36),[5] which covers eight domains of health status: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. The SF-36 score ranges from 0 (worst) to 100 (best) and norm based scoring is available to compare different populations. Two summary measures, representing the physical component of HRQoL (physical component scale; PCS) and the mental component of HRQoL (mental compo-

nent scale; MCS) are available. Both scales cover all HRQoL domains but more weight is given to physical functioning, role-physical, bodily pain and general health in the PCS, whereas more weight is given to vitality, social functioning, role-emotional and mental health in the MCS. The SF-36 was filled out every 3 months in the first two years of treatment and yearly thereafter. A clinically important improvement from baseline for RA patients has previously been established as a minimum of 2.5 to 5 points improvement for the two summery measures.[6]

Statistical methods

Statistical analyses were performed with the software program SPSS version 20.0 (SPSS, Chicago, Illinois). Linear mixed models (LMM) were used to investigate the association between disease activity (levels) and HRQoL over time, while correcting for within patient correlation. For all analyses the unstructured covariance matrix was used, which does not assume a specific covariance structure and estimates every variance and correlation.

Two continuous outcomes, both of which normally distributed, were used for all analyses: the PCS and the MCS. Three models with these outcomes and the following independent variables were used: 1) disease activity category, 2) delta DAS (absolute), previous DAS and previous PCS or MCS score and 3) change in disease activity category (remission to LDA and vice versa) and previous PCS or MCS score.

For the first and third model, patients were categorized according to their disease activity category: high disease activity, low disease activity (based on the DAS), or remission.[7] Remission was defined as DAS<1.6,[8] or, in a separate analysis, according to the ACR/EULAR remission criteria.[9] Patients were first divided into ACR/EULAR remission yes/no, and patients not in ACR/EULAR remission were then classified into low or high disease activity depending on their DAS. The ACR/EULAR remission criteria were not designed to compare against DAS categories, but as there is no alternative classification method that allows for comparison of ACR/EULAR remission against other levels of disease activity we used this approach. In model 3, all possible changes were included in the model. We first used staying in low disease activity as reference category and then staying in remission and will only report on changing from low disease activity to remission and vice versa. Time was added as categorical covariate in all models in order to estimate the effect for each time point separately. The baseline visit was excluded because none of the patients were in remission at this visit. The following potential baseline confounders were considered: age, gender, HAQ, DAS, erosions (yes/no), anti-citrullinated protein antibodies, duration of complaints at inclusion, smoking, body mass index (BMI), alcohol intake and treatment group. None of the potential confounders importantly altered β-estimates or p-values when added to the model as separate variable, so these were not included in the final models. Values for mean HRQoL at each time point per disease activity category were calculated using Estimated Marginal Means.*(figure 1)*

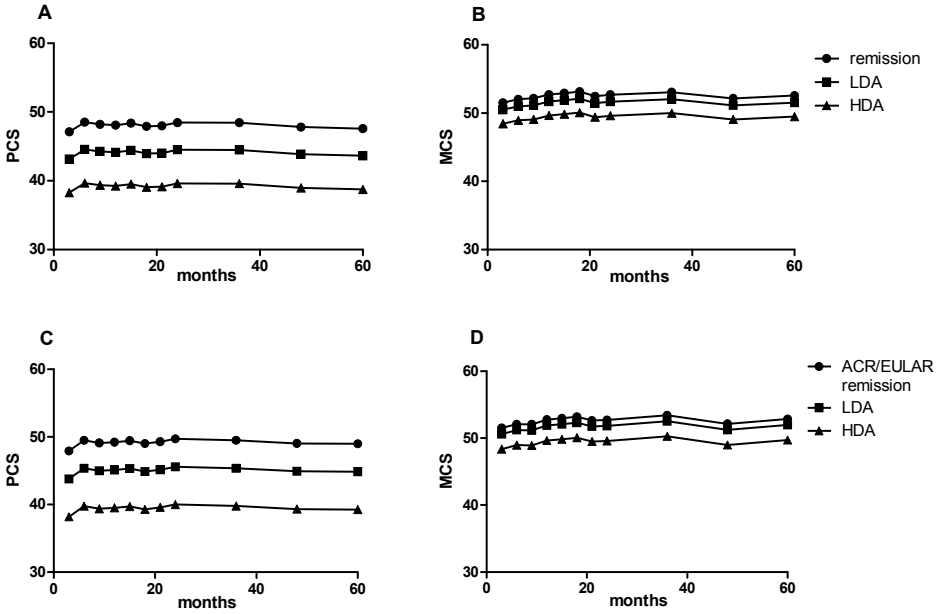

Figure 1: Health Related Quality of Life (HRQoL) per disease activity level over time depicted as mean Physical Component Scale score (PCS, panel a and c) and mean Mental Component Scale score (MCS, panel b and d) over time

RESULTS

In total 508 patients with a mean (SD) DAS at baseline of 4.4 (0.9) were included. Mean PCS (SD) was 38.8 (7.9) and mean MCS at baseline was (47.0 (11.4). At year 5, DAS was reduced to a mean (SD) level of 1.7 (0.8) while PCS and MCS had improved to a mean (SD) level of 44.8 (9.8) and 52.4 (8.6) respectively. Over 5 years (excluding the baseline evaluation), DAS-remission was recorded in 34% of the evaluations, while ACR/EULAR remission was recorded in 15%.(*table 1*)

Table 1: percentage of patients per disease activity category using two remission definitions for year 0-5 excluding the baseline visit

	Remission: DAS<1.6 (n visits =4941)	ACR/EULAR Remission criteria (n visits=4499)*
Remission	1667 (34%)	662 (15%)
Low disease activity	1704 (35%)	2384 (53%)
High disease activity	1570 (32%)	1453 (32%)

DAS disease activity score, *n* number, *ACR* American College of Rheumatology, *EULAR* European League Against Rheumatism

*For 442 visits, patients could not be classified because of missing values for C-reactive protein

Low disease activity: DAS ≤2.4, but not remission, High disease activity: DAS>2.4

Absolute disease activity scores in relation to QoL scores

Remission (DAS<1.6) was associated with a clinically relevant higher PCS than higher levels of disease activity, with a dose response relationship. The difference in PCS when in remission with PCS when in LDA (ß) was 4.0, and the difference with HDA 8.8, all p<0.001. (*table 2, figure 1*) Likewise, DAS categories with lower DAS were associated with higher MCS, although differences were smaller: LDA ß=1.0, HDA ß=3.1. Repeating the analyses with remission according to the ACR/EULAR remission criteria gave similar results.(*table 2)* The univariable analysis showed that DAS category, gender, time, treatment group, alcohol intake, BMI and baseline DAS were also associated with outcome PCS, and DAS category, time, gender, baseline erosiveness (yes/no), baseline smoking status and baseline DAS were univariable predictors for MCS. Of the possible confounding variables none had a significant effect on the ß-estimates per disease activity category when added separately to the model, neither on the outcome PCS nor on MCS.

Changes in disease activity scores in relation to changes in HRQoL scores Absolute changes in DAS scores were significantly associated with changes in both PCS and MCS. Patients showed an increase of 4.6 (95% CI 4.4;4.8) points in PCS when decreasing 1 point in DAS, independent of their previous DAS score and previous PCS (p<0.001). Similar results are seen for the MCS, however this difference is smaller: 1.6 (95% CI 1.3;1.9) points (p<0.001) improvement in MCS per 1 point decrease in DAS. The interaction term between previous DAS and DAS change was not significant, implying that the relationship between change in DAS and change in PSC/MCS is independent of the preceding DAS level.

Changes in DAS category in relation to change in PCS and MCS

For patients who had LDA, achieving remission was associated with a significant improvement in PCS of 3.8 points, when compared to patients who stayed in LDA, but

Table 2: difference in absolute physical component scale score and mental component scale score for patients in low and high disease activity compared to patients in remission, defined as DAS<1.6 or according to the ACR/EULAR remission criteria

	PCS		MCS	
Remission	*ref (defined as DAS<1.6)*	*ref (defined according to ACR/EULAR criteria)*	*ref (defined as DAS<1.6)*	*ref (defined according to ACR/EULAR criteria)*
LDA	4.0 (3.5;4.4)	4.1 (3.5;4.8)	1.0 (0.5;1.5)	0.9 (0.2;1.6)
HAD	8.8 (8.3;9.4)	9.7 (9.0;10.5)	3.1 (2.5;3.7)	3.1 (2.3;3.9)

PCS physical component scale score Short form 36 (SF36), *MCS* mental component scale score SF36, *DAS* disease activity score, *LDA* low disease activity (DAS ≤2.4, but not remission), *HDA* high disease activity (DAS>2.4) , *ref* reference

Data are presented as ß estimates (95% CI), representing the estimated difference with the reference category in PCS or MCS score

no improvement in MCS.(*table 3*) Patients who had been in remission but flared to LDA showed a 4.0 point deterioration in PCS when compared to patients who stayed in remission, and no change in MCS.

Table 3: change in component score (physical component scale score and mental component scale score) when achieving remission from low disease activity, and loosing remission to low disease activity, with remission defined as *DAS<1.6 and **according to the ACR/EULAR remission criteria

	PCS		MCS	
Staying in low disease activity	*ref*	*ref*	*ref*	*ref*
Achieving remission from low disease activity	3.8 (3.0;4.5)*	4.0 (3.1;4.9)**	0.5 (-0.3;1.3)*	1.0 (-0.01;2.0)**
Staying in remission	*ref*	*ref*	*ref*	*ref*
Loosing remission to low disease activity	-4.0 (-4.8;-3.2)*	-4.0 (-5.1;-2.9)**	-1.2 (-2.1;-0.3)*	-0.7 (-1.9;0.5)**

PCS physical component scale score Short form 36 (SF36), *MCS* mental component scale score SF36, *DAS* disease activity score, *ref* reference
Data are presented as ß estimates (95% CI), representing the estimated difference in change in PCS or MCS score relative to the reference category

DISCUSSION

In this disease activity targeted treated cohort, lower disease activity was associated with better health related quality of life (HRQoL), both in the physical and mental component scale, although differences in the latter were smaller. This association was independent of the previous disease activity level and related to the final level of disease activity. A change in disease activity resulted in a change in HRQoL. We found that a clinically significant improvement of quality of life (in the physical component scale) was achieved when patients who were in a state of LDA went on to achieve remission.

To date, remission is recommended to be the optimal treatment target in RA patients,[2] but aiming for remission could increase the costs of treatment and the risk of side effects. In patients who have already achieved LDA, it is questionable if a further suppression of disease activity to a level of remission (whether based on a composite score threshold such as <1.6 in the disease activity score or based on the boolean ACR/EULAR remission criteria), also results in a further improvement in quality of life. This we have shown was indeed the case (and reversely, there was a deterioration in HRQoL if disease activity deteriorates from remission to LDA) in this LDA targeted cohort.

Previous studies have shown a cross-sectional correlation between active disease and impaired quality of life measured with generic HRQoL instruments,[10,11] and a dose-response effect of the different disease activity categories.[12,13] In longitudinal analyses over 2 years and over 10 years, it has already been suggested that an improvement in disease activity is associated with better HRQoL.[14,15] This association over a long time

span may be influenced by other factors such as damage progression. As disease activity may fluctuate over time, we focused in our longitudinal analysis on shorter time intervals, and within these shorter time interval we found that improving in DAS and more specifically achieving remission is associated with improved HRQoL.

There are several limitations to our study. A DAS<1.6 may not denote true remission,[3] and the distinction with LDA (DAS ≤2.4) is relatively arbitrary. We repeated the analysis using the ACR/EULAR remission criteria, but here we were limited by the absence of associated ACR/EULAR low disease activity criteria. Instead, we again compared with 'not in ACR/EULAR remission' with established DAS categories for increased disease activity. Although according to the ACR/EULAR criteria, less patients were in remission than when using DAS remission, this did not result in a difference in the association between disease activity and HRQoL.

Second, although the association between disease activity category and HRQoL was independent of a number of patient characteristics, there might still have been residual confounding, for example caused by co-morbidity. Therefore, we cannot conclude that the achievement of remission *causes* patients to have better health related quality of life. There could be unmeasured patient traits related both to disease activity and HRQoL. A randomized clinical trial comparing a treatment strategy aiming at LDA with a strategy aimed at remission using the same therapies would help to answer this question.

Although the change in MCS associated with achieving remission from LDA was statistically significant, it was not clinically significant. However, the mental component was also less impaired from the outset. The finding that disease activity shows a stronger relation with the physical than the mental component scale is in line with previous analyses from this study, where improvement of disease activity was associated with a smaller improvement of the MCS than the PCS,[16] and data from other cohorts.[17,18] This may be caused by the fact that in particular the mental component of HRQoL could be affected by other variables such as pain experience, psychological comorbidity, mental status, coping strategies and social networks. Also, MCS may depend more on stable patient traits such as optimism than on disease characteristics, and therefore show less variation.[19-22]

In conclusion, we have shown that a decrease in disease activity in patients with RA is associated with better HRQoL and that achieving remission after being in LDA is associated with achieving clinically significant improvement of HRQoL. This may suggest that remission is the preferred target of treatment and have implications for future (research on) goal setting in the treatment of RA.

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Chapter 11

Summary and general discussion

In this thesis, a number of longer-term outcomes of rheumatoid arthritis and their determinants, as well as the possibility of drug-tapering when the treatment goal of low disease activity was achieved, have been discussed.

In chapter 1, the general introduction, the prevalence and clinical characteristics of rheumatoid arthritis are discussed. As patients with RA have a high risk of functional disability, especially when risk factors for an unfavorable disease course such as anti-citrullinated protein antibodies are present, rapid suppression of disease activity is important. This can be achieved by treating patients early in the disease course and by switching the therapeutic strategy when the response is insufficient. Patients treated with biologic anti-rheumatic drugs often show a good clinical response and minimal joint damage progression. In current recommendations biologics are advised to be introduced after failing on one or more conventional anti-rheumatic drugs (so called DMARD), but this might lead to suboptimal treatment results. In addition it has been shown that setting a treatment goal, frequent treatment evaluation with a composite index such as the disease activity score (DAS), and changing or intensifying treatment when the treatment goal has not been achieved, leads to better clinical and structural outcomes.

THE BEST COHORT

The data described in chapters 2-7 and in chapter 10 are from the BeSt cohort. In the BeSt study, 508 DMARD naïve early RA patients were included and followed up for a total of 10 years. Randomized to one of four treatment strategies (sequential monotherapy, step-up combination therapy, initial combination therapy with prednisolone or initial combination therapy with infliximab), they were treated according to a dynamic treatment protocol aiming at low disease activity. The initial combination therapy groups showed a more rapid improvement of disease activity and functional ability, and less small joint damage progression up and until year 5 of the study.[1] Although treatment was steered at low disease activity, 48% was in clinical remission (DAS<1.6) at year 5. Drug-tapering to maintenance dose once the treatment goal had been achieved was incorporated in the initial protocol, and from year 3 these patients, when in remission for at least 6 months, were required to also taper the last drug, to drug free remission. It was shown that long-term discontinuation of TNF-blocker infliximab was possible, both in patients initially treated with infliximab and in patients treated after failing on other treatment steps.[2] Drug-free remission was achieved in 23% of patients who completed the first 5 years.[1]

STRUCTURAL OUTCOMES AND FUNCTIONAL DISABILITY

Large joint damage

In older cohorts, large joint damage is an important contributor to functional disability in RA patients.[3] Large joint damage usually develops later in the disease course than small joint damage,[4,5] Thus, prevention of large joint damage is an important treatment goal which may be achieved if disease activity is effectively suppressed. In the BeSt cohort, patients were treated earlier than in the older cohorts that reported on large joint damage and disease activity was rapidly and effectively suppressed in most patients. It is unknown whether and how much large joint damage occurs in those circumstances and whether large joint damage still causes functional disability.

For small joints of the hands and feet it has been shown that local swelling and pain is associated with later local damage.[6] In chapter 2 we asked whether local swelling and tenderness in large joints in the first two years of treatment, when disease activity was highest, was associated with local joint damage after 8 years of disease activity-steered treatment. We found at least minimal large joint damage in 1 joint (Larsen score ≥1) in 64% of patients. Local swelling during the first two years was associated with local damage, independent of baseline characteristics, treatment strategy and the disease activity score over these years. The attributable risk of local swelling was 8 to 25 (depending on the duration of swelling) per 100 joints. The association between local tenderness and local damage was weaker. Large joint damage showed a weak, but significant correlation with functional disability. As intra-articular corticosteroid injections in the MCP joints were shown to be associated with less erosions on MRI, such injections in large joints might play a role in the prevention of damage following joint swelling and tenderness. This could be especially relevant in patients with an increased baseline risk of large joint damage, for example ACPA and/or RF positive patients. Further research comparing joints that were or were not treated with intra-articular corticosteroid injections could provide more insight in the possible structural benefits of these injections.

In clinical practice, small joint damage is often monitored more frequently than large joint damage, and the treatment strategy is sometimes changed because of small joint damage progression despite adequate control of disease activity. Previously an association between small and large joint damage was shown,[3,7] indicating that these treatment decisions could also be beneficial for the prevention of large joint damage. In chapter 3, the large joint damage distribution pattern and the association between small and large joint damage in our DAS-targeted treated cohort was evaluated. Despite limited large joint damage with a median Larsen score of 1 (equal to minimal damage in 1 large joint), there was a significant association between small and large joint damage progression after 8 years treatment in the BeSt cohort The distribution pattern of large joint damage

was symmetrical, corresponding with the clinical pattern of joint involvement in RA patients. Despite early suppression of disease activity, the percentage of patients with any damage was comparable to the percentage reported in older cohorts,[3,7] although the extent of damage was smaller in the BeSt cohort. Frequent monitoring of small joint damage and treatment adjustments in case of damage progression might also prevent large joint damage.

Rapid radiological progression

Initial combination therapy was shown to lead to more rapid disease suppression and less radiological damage progression in the first years of treatment, but has the potential downsides of an increased risk of side effects and, in the case of biologics, high costs. Matrix models using baseline patient and/or disease characteristics were designed to predict what the risk of an adverse outcome was with various initial therapies.[8,9] These prediction models used radiological progression of at least 5 points (SHS) in the first year of treatment, rapid radiological progression (RRP), as outcome. However, with the new drugs and treatment strategies, damage progression was shown to be no longer linear.[1] Progression may be so well suppressed that patients do not feel the consequences of minimally damaged joints, and are only hampered by inflamed joints. It was unknown whether RRP does precede significant damage in later years and is associated functional disability. In chapter 4, functional disability and radiological damage progression after 8 years of treatment were compared in patients with and without RRP. Patients with RRP had worse functional ability, but also higher disease activity over 8 years. After adjustment for disease activity, the difference in functional ability was smaller than the clinically relevant difference.[10] There was however a clinically relevant difference in functional ability between patients with at least 9.5 points progression in the first year, the top 10% of patients with damage progression, and the other 90%, after adjustment for disease activity. In patients with RRP further damage progression in years 1-8 was equal to the smallest detectable difference of 5 points. The damage progression in years 1-8 in the patients with the top 10% of damage progression in year 1 was larger: 15.5 points. In contrast to older RA cohorts,[11] in the BeSt cohort functional ability has not deteriorated over time. We cannot predict if or when after longer follow-up the difference in functional ability between patients with and without RRP will become clinically relevant. The cut-off of 5 points in the first year may possibly be too low, and should instead be around 10 points.

TREATMENT RESPONSE

Anti-citrullinated protein antibodies

ACPA are associated both with, in patients with early arthritis, a risk for developing RA and, in patients with RA, a more severe disease course.[12] ACPA-positive patients in older cohorts had higher disease activity, worse functional ability and more joint damage progression.[13-19] It is unknown whether ACPA are associated with response to therapy in a tight control setting with treatment aimed at low disease activity. In chapter 5, the association between ACPA and treatment response was evaluated in the BeSt cohort. We found no differences in clinical outcomes for ACPA-positive patients compared to ACPA-negative patients, except that more ACPA-negative than ACPA-positive patients were able to achieve and maintain drug-free remission. Although the disease activity appeared to be equally suppressed in ACPA-positive and ACPA-negative patients, in ACPA-positive patients, but only if they were treated with initial monotherapy, this was associated with more radiological damage progression over 8 years. These results indicate that ACPA-positive patients benefit from initial combination therapy. The difference in the association between changes in disease activity and joint damage progression suggest that aiming at even lower disease activity (eg remission) in ACPA-positive patients could also lead to better outcomes. Also it may be particularly worthwhile to monitor radiological progression ACPA-positive patients and let that influence treatment decisions.

Body mass index and treatment response

It has been shown that patients with more fat tissue and consequently a high BMI show more inflammation.[20,21] In theory, these patients might respond less well to anti-inflammatory medication than patients with a normal BMI. This was indeed shown in patients treated with TNF-blockers,[22,23] but the difference in treatment response between patients with a high and a normal BMI might not be specific for TNF-blockers. In chapter 6, we examined the association between BMI and treatment response in all treatment groups of the BeSt cohort. We showed that patients with a high BMI had a higher risk of insufficiently responding to initial combination therapy with either TNF-blocker infliximab or with prednisolone. In patients who received delayed infliximab treatment, we found similar results. The fact that there was no increased risk of insufficient response to initial monotherapy might be explained by the fact that so many patients were non-responders to this strategy, making it harder to study the role of individual risk factors. We hypothesized that the decreased response was caused by cytokines produced by fat tissue, but interestingly we found no signs and symptoms of increased inflammation in patients with a high BMI. Instead, patients with a high BMI had higher pain scores and a worse assessment of their global health. Possibly a difference in the pain response

between patients with high and normal BMI, which has been previously shown in other studies,[24,25] could explain at least part of the difference in response to medication. This would be relevant for clinical practice, as a change in anti-inflammatory medication might not be beneficial for patients who appear to have high disease activity through pain associated with high BMI. Our results would have to be confirmed in a cohort that also has cytokine data available, to further support this hypothesis.

DRUG DISCONTINUATION

Infliximab

Initial combination therapy with infliximab resulted in earlier improvement of disease activity and functional ability and less radiological damage progression in the first years of the disease. However, as TNF-blockers have high costs and are associated with an increased risk of serious infections, it would be best if these could be discontinued after the treatment target has been met. Previous studies have shown that this could indeed be possible in some patients,[26-29] but other patients will experience an increase in disease activity after discontinuation. Restarting the medication may lead to allergic reactions[30] and regaining low disease activity or remission may take time, or this may not happen at all. In chapter 7 we looked at the possibility of discontinuation of initial and delayed infliximab in the BeSt study and at predictors of successful discontinuation. Discontinuation after achieving low disease activity for at least 6 months was possible in 45% of all patients treated with infliximab. In 80% of patients disease activity remained low for at least 1 year after this. After a median follow-up duration of 7.2 years, 52% still had low disease activity without restarting infliximab. These results may not resemble daily practice and might be an overestimation of the success of infliximab discontinuation, since in daily practice TNF inhibitors are almost restricted to use in patients who previously failed on at least methotrexate and one other synthetic DMARD. Such patients, who received 'delayed infliximab' in the BeSt study less often could discontinue infliximab than patients who received infliximab as initial treatment and they had more disease flares after infliximab discontinuation even though they had a shorter follow-up period. Restarters usually regained low disease activity and infusion reactions did not occur more often than in patients who first started treatment with infliximab. Smoking, the presence of HLA shared epitope (SE) and a treatment duration of at least 18 months were predictive of flare of disease activity after discontinuation, also after including treatment timing in the model. Although ACPA positivity was not an independent predictor, replacing SE with ACPA gave similar results for patients with no risk factors, making the model more useful for clinical practice. The rate of successful discontinuation after 1 year was somewhat higher than in previous studies. This might be explained by the differences

in patients studied: most other studies included patients with longer disease duration and most had failed on previous treatment, whereas we included patients who received infliximab as first treatment. Another possible explanation is that patients in our study continued targeted treatment with methotrexate monotherapy after infliximab discontinuation. In contrast to most patients outside a clinical trial, patients in the BeSt study had been informed and expected that TNF-blockers would be discontinued once low disease activity had been achieved before starting treatment. Regardless of whether or not an increase in disease activity caused infliximab to be restarted in our study, radiological damage progression was rare in year 1 and functional ability was stable in years 1 and 3. There was however a decrease of functional ability 5 years after discontinuation in patients who had flared when compared to their functional ability at the moment of discontinuation, which was not observed in the group that did not flare. This might be a reflection of the selection of patients with a more severe disease profile, instead of an effect of discontinuation and reintroduction of infliximab. Overall, discontinuation of TNF-blockers is safe and has good short-term outcomes, so it could be tried, especially in non-smoking, ACPA-negative patients who showed a rapid response to treatment.

Biological therapies

In chapter 8 we describe a number of studies that included in their protocol discontinuation of biological therapies after the treatment goal of low disease activity or remission had been achieved.[29,31-35] Loss of remission or low disease activity was reported in 3% to just over 50% of patients during follow-up durations varying from 3 months to over 7 years. On a group level, there was no significant joint damage progression in the year after discontinuation. One study found a clinically relevant difference in functional ability between patients who flared in the first year after discontinuation and patients who did not,[29] although three other studies found no deterioration of functional ability.[27,33,35] Retreatment was successful in 75-100% of patients. Mild infusion reactions did occur in a number of patients, although this number was not higher than during initial treatment.[35] In one study, anti-drug-antibodies were measured and found in 10% of patients compared to none of the patients who had not discontinued, but no clinical consequences of these antibodies were reported.[31] Current recommendations for the treatment of patients with RA suggest that in some patients biologic therapies may be discontinued, but cannot give evidence based advice on when and in which patients. The described studies show that (temporary) discontinuation is possible in at least 50% of patients. Patients should be monitored regularly after drug discontinuation so that treatment can be restarted when disease activity increases, and/or joint damage progression is present. In particular patients with longstanding disease and patients outside of clinical trials where drug discontinuation was an announced part of the treatment protocol, might be reluctant to discontinue their biologic agent when this was effective in lower-

ing their disease activity, sometimes for the first time since their diagnosis. Low expectations of success might influence the results after drug discontinuation. This might be especially relevant in countries where biologics can only be given to patients who failed on synthetic DMARD. Expectation management could therefore play an important role in treatment and discontinuation strategies.

Drug-free remission

In chapter 9 we gave an overview of recent studies describing discontinuation of the last DMARD in patients who were in remission: three clinical trials and one report on two cohort studies.[36-39] Between 10 and 23% of patients were able to discontinue all DMARD, with lower percentages in the cohort studies than in the clinical trials. Around 45% of patients had to restart medication after a disease flare, but these patients had similar functional ability and radiological damage progression as patients in sustained drug-free remission. One of the two studies did find higher disease activity in restarters,[39] but in the DAS-targeted BeSt study, the majority of patients regained remission or at least had low disease activity shortly after reintroduction of their DMARD.[36] RF, ACPA and HLA shared epitope negativity and short symptom duration before treatment initiation were independent predictors of successful drug discontinuation.[36,37,39] As discontinuation and reintroduction of DMARD have good short-term clinical and structural outcomes, the fact that patients with these risk factors more often have to restart medication after achieving drug-free remission does not mean drug discontinuation cannot be tried. The benefits of a 'drug holiday' could outweigh the potential downside of a disease flare. Further research should point out whether ameliorations in treatment strategies such as initiation of treatment even earlier in the disease course and then starting with combination therapy in those patients could result in even higher drug-free remission percentages with good long-term clinical and structural outcomes.

HEALTH RELATED QUALITY OF LIFE

Health related quality of life has been shown to improve with RA treatment.[40-43] Current guidelines advise to treat to target with remission or low disease activity as treatment goal.[44] It is unknown whether remission is associated with better health related quality of life than low disease activity. In chapter 10 we found that patients who were in remission indeed had better HRQoL than patients who had low disease activity, and that an increase of the DAS was associated with a deterioration of HRQoL, irrespective of the previous DAS. Patients who had been in low disease activity and achieved remission had an improvement of their HRQoL when compared to when they remained in low disease activity. These findings suggest that besides being associated with better functional

ability and less damage progression, achieving remission could result in better HRQoL. However, there might be patient characteristics that cause some patients to achieve remission where others maintain low disease activity that we were not able to adjust for in our analyses. Further research should point out whether achieving remission *causes* an improvement of HRQoL.

FUTURE CHALLENGES

On a group level, the introduction of early treatment, combination therapy and treatment to target have markedly improved the short-term and longer-term outcomes of patients with rheumatoid arthritis. This thesis has however shown that there is still room for improvement and future research in a number of areas involving the treatment of early RA.

There is still a relatively high number of patients with large joint damage, which can cause irreversible functional disability, although the extent of damage is less than in older patient cohorts after comparable follow up periods. As early local synovitis is associated with later local damage, research focusing on the role of local treatment in large joint damage progression could offer a new therapeutic option to prevent large joint damage. Second, research should focus on those patients who have significant damage progression in the first year of treatment (rapid radiological progression, or RRP) despite treatment aiming at low disease activity. The fact that the presence of baseline damage is associated with RRP might indicate that treatment should have been initiated earlier in the disease course in these patients. The new RA classification criteria can be used to select patients for clinical trials in order to evaluate the benefits of earlier initiation of treatment in this subpopulation. On the other hand, the presence of joint damage before treatment initiation could also be a marker for having risk factors for further joint damage progression. In that case, these patients might benefit from setting a more stringent treatment target. This is also suggested by the fact that the presence of ACPA, one of the risk factors for RRP, is associated with more joint damage progression per point DAS increase. More research is needed to support the hypothesis that a more stringent treatment goal will be beneficial for these high risk patients, and possibly for all RA patients, as is suggested in the EULAR recommendations.[44] Intuitively, the ultimate treatment goal would be remission in all RA patients, but it has never been proven that treatment *aimed at* remission will lead to better clinical, structural and patient reported outcomes in all patients than treatment aimed at low disease activity. Unnecessary treatment adjustments using too many anti-rheumatic drugs might be the downside of such a remission targeted treatment strategy, with high costs, potential side effects, unfulfilled expectations and ultimately worse outcomes. A randomized trial comparing

aiming for either low disease activity or remission, with block randomization for autoantibody status to allow for a stratified analysis could answer the question whether aiming for remission is indeed superior to aiming for low disease activity.

CONCLUSION

This thesis shows that continued low disease activity steered treatment is possible and leads to the maintenance of good functional ability in the majority of patients during 8 years of follow-up. Patients with large joint damage and/or rapid radiological progression had slightly higher disease activity over 8 years of follow-up than patients who did not. This indicates that adequate disease control plays an important role in maintaining functional ability. One way to achieve this is to initiate combination therapy early in the disease course. The potential downsides, an increased risk of side-effects and high costs, can be minimized by tapering medication as soon as the treatment goal has been achieved and maintained for a period of around 6 months. With the use of known markers of disease course severity and response to medication and the search for new (bio) markers, treatment can be further personalized in order to avoid withholding effective treatment until other strategies are unsuccessfully explored, and on the other hand prevent overtreatment. Another important step towards personalizing RA treatment is further unraveling the pathways involved in ACPA-positive and ACPA-negative disease. These might be different and therefore require different treatment strategies, as is suggested by the difference in joint damage progression in patients initially treated with monotherapy. Ultimately, early personalized treatment to target should lead to rapid suppression of disease activity and then drug tapering while good functional ability and joint integrity are maintained in all RA patients.

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Chapter 12

Nederlandse samenvatting

In dit proefschrift is een aantal middellange termijn resultaten en determinanten van reumatoïde artritis, alsmede de mogelijkheid van het afbouwen van medicatie na het bereiken van het behandeldoel van lage ziekteactiviteit besproken.

In hoofdstuk 1, de algemene inleiding, worden de prevalentie en klinische kenmerken van reumatoïde artritis beschreven. Omdat patiënten met RA een verhoogd risico van disfunctioneren hebben, vooral als risicofactoren voor een ongunstig ziekteverloop zoals antilichamen tegen gecitrullineerde eiwitten (zogenaamde ACPA) aanwezig zijn, is snelle onderdrukking van ziekteactiviteit belangrijk. Dit kan worden bereikt door patiënten vroeg in het ziekteverloop te behandelen en de behandelstrategie aan te passen wanneer de reactie op medicatie onvoldoende is. Patiënten die behandeld worden met biologische antireumatische geneesmiddelen vertonen vaak een goede klinische respons en minimale gewrichtsschade. In de huidige aanbevelingen wordt geadviseerd om pas nadat patiënten gefaald hebben op één of meer synthetische antireumatische geneesmiddelen (zogenaamde synthetische DMARDs) te starten met biologische antireumatische middelen, maar dit kan leiden tot suboptimale behandelresultaten. Daarnaast is gebleken dat het instellen van een behandeldoel, regelmatige evaluatie van de behandeling met een samengestelde score, zoals de disease activity score (DAS), en het aanpassen of intensiveren van de behandeling wanneer het doel van de behandeling niet is bereikt, leidt tot betere klinische en structurele resultaten.

HET BEST COHORT

De gegevens in de hoofdstukken 2-7 en in hoofdstuk 10 zijn afkomstig uit het BeSt cohort. In de BeSt studie werden 508 DMARD naïeve vroege RA patiënten opgenomen en gevolgd gedurende 10 jaar. Na randomisatie in één van de vier behandelstrategiegroepen (sequentiële monotherapie, step-up combinatietherapie, initiële combinatietherapie met prednison of initiële combinatietherapie met infliximab), werden zij behandeld volgens een dynamisch behandelprotocol gericht op lage ziekteactiviteit. De initiële combinatietherapie groepen vertoonden een snellere verbetering van ziekteactiviteit en functioneren, en minder schade aan de kleine gewrichten tot en met jaar 5 van de studie. Hoewel de behandeling werd gestuurd op lage ziekteactiviteit, was 48% in klinische remissie (DAS <1,6) in jaar 5. Het afbouwen van medicatie tot de onderhoudsdosering zodra het behandeldoel bereikt was, was opgenomen in het oorspronkelijke protocol. Vanaf jaar 3 konden deze patiënten, wanneer remissie gedurende ten minste 6 maanden was bereikt, ook hun laatste medicijn afbouwen, om medicatievrije remissie te bereiken. Er werd aangetoond dat het langdurige stoppen van TNF-blokker infliximab, een biologische DMARD, mogelijk was, zowel bij patiënten aanvankelijk behandeld met

infliximab als bij patiënten die met infliximab behandeld waren nadat zij onvoldoende gereageerd hadden op andere behandelstappen. Medicatievrije remissie werd bereikt bij 23% van de patiënten in de eerste 5 jaar.

STRUCTURELE UITKOMSTEN EN DISFUNCTIONEREN

Schade aan de grote gewrichten

In oudere cohorten leverde schade aan de grote gewrichten een belangrijke bijdrage aan disfunctioneren in patiënten met RA. Schade aan de grote gewrichten ontstaat meestal later in het ziekteproces dan schade aan de kleine gewrichten. Daarom is het voorkomen van grote gewrichtsschade een belangrijk behandeldoel, dat mogelijk bereikt kan worden door voldoende onderdrukking van de ziekteactiviteit. In het BeSt cohort werden patiënten eerder behandeld dan in de oudere cohorten die over schade aan de grote gewrichten gerapporteerd hebben en de ziekteactiviteit werd snel en effectief onderdrukt in de meerderheid van de patiënten. Het is niet bekend of, en hoeveel schade aan de grote gewrichten optreedt in deze omstandigheden en of schade aan de grote gewrichten nog steeds disfunctioneren veroorzaakt. Voor de kleine gewrichten van handen en voeten is aangetoond dat plaatselijke zwelling en pijn geassocieerd is met latere plaatselijke schade. In hoofdstuk 2 hebben we bekeken of plaatselijke zwelling en pijn in de grote gewrichten in de eerste twee jaar van de behandeling, toen de ziekteactiviteit het hoogst was, geassocieerd was met plaatselijke schade aan de grote gewrichten na 8 jaar ziekteactiviteit gestuurd behandelen. We vonden ten minste minimale schade aan 1 groot gewricht (Larsen score ≥1) in 64% van de patiënten. Plaatselijke zwelling gedurende de eerste twee jaar was geassocieerd met latere plaatselijke schade, onafhankelijk van kenmerken van patiënten die bij start van behandeling aanwezig waren, behandelstrategie en de ziekteactiviteit gedurende deze jaren. Het attributief risico van plaatselijke zwelling was 8 tot 25 (afhankelijk van de duur van de zwelling) per 100 gewrichten. De associatie tussen plaatselijke pijn en plaatselijke schade was minder sterk. Schade aan de grote gewrichten vertoonde een zwakke, maar significante correlatie met disfunctioneren. Aangezien het is aangetoond dat gewrichtsinjecties met corticosteroïden in de MCP gewrichten geassocieerd zijn met minder erosies op de MRI, zouden deze injecties in grote gewrichten een rol kunnen spelen in het voorkomen van schade die volgt op zwelling en pijn aan deze gewrichten. Dit kan vooral van belang zijn in patiënten met een verhoogd basisrisico van schade aan de grote gewrichten, bijvoorbeeld ACPA en/of reumafactor positieve patiënten. Nader onderzoek waarin gewrichten worden vergeleken die wel of niet behandeld zijn met gewrichtsinjecties met corticosteroïden zou meer inzicht kunnen geven in de mogelijke voordelen op structurele uitkomsten van deze injecties.

In de praktijk wordt radiologische schade aan de kleine gewrichten vaker geëvalueerd dan schade aan de grote gewrichten, en de behandelstrategie wordt soms aangepast vanwege toename van schade aan de kleine gewrichten ondanks voldoende onderdrukking van de ziekteactiviteit. Eerder werd een associatie aangetoond tussen kleine en grote gewrichtsschade, wat er op wijst dat deze beslissingen ook positieve gevolgen kunnen hebben voor het voorkomen van grote gewrichtsschade. In hoofdstuk 3 werden het patroon van grote gewrichtsschade en de associatie tussen schade aan de kleine en grote gewrichten geëvalueerd. Ondanks geringe schade aan de grote gewrichten met een mediane Larsen score van 1 (gelijk aan mimimale schade aan 1 groot gewricht) was er een significante associatie tussen schade aan de kleine en grote gewrichten na 8 jaar behandeling in het BeSt cohort. Het patroon van grote gewrichtsschade was symmetrisch, wat correspondeert met het klinische patroon van betrokkenheid van de gewrichten in RA patiënten. Ondanks vroege onderdrukking van de ziekteactiviteit was het percentage patiënten met schade aan de grote gewrichten vergelijkbaar met het percentage dat in oudere cohorten gerapporteerd werd, hoewel de hoeveelheid schade kleiner was in het BeSt cohort. Frequente evaluatie van radiologische schade aan de kleine gewrichten en aanpassingen van de behandeling wanneer de schade toeneemt zou ook schade aan de grote gewrichten kunnen voorkomen.

Snelle toename van radiologische schade

Het is aangetoond dat initiële combinatietherapie leidt tot snellere onderdrukking van ziekteactiviteit en remming van radiologische schade in de eerste jaren van de behandeling, maar het heeft de mogelijke nadelen van een verhoogd risico op bijwerkingen en, in het geval van biologische antireumatische middelen, hoge kosten. Matrix modellen waarin kenmerken van de patiënt en de ziekte bij diagnose worden gebruikt, werden ontworpen om het risico op ongewenste uitkomsten met verschillende initiële therapieën te voorspellen. Deze voorspelmodellen gebruikten toename van radiologische schade van ten minste 5 punten in het eerste jaar van de behandeling (zogenaamd RRP) als uitkomst. Met de nieuwe medicatie en behandelstrategieën is de toename van radiologische schade over de tijd echter niet meer lineair. Toename van schade zou zo goed onderdrukt kunnen zijn dat patiënten de gevolgen van minimaal beschadigde gewrichten niet meer voelen, en alleen beperkt zijn door ontstoken gewrichten. Het was onbekend of RRP vooraf gaat aan significante schade in latere jaren en geassocieerd is met disfunctioneren. In hoofdstuk 4 werden functioneren en toename van radiologische schade gedurende 8 jaar behandeling vergeleken in patiënten met en zonder RRP. Patiënten met RRP functioneerden slechter, maar hadden ook hogere ziekteactiviteit gedurende 8 jaar. Na correctie voor ziekteactiviteit was het verschil in functioneren kleiner dan het klinisch relevante verschil. Er was echter wel een klinisch

relevant verschil in functioneren tussen patiënten met ten minste 9,5 punt toename van schade in de kleine gewrichten in het eerste jaar, de top 10% patiënten met toename van schade, en de andere 90%, na correctie voor ziekteactiviteit. Patiënten met RRP hadden van jaar 1-8 een toename van schade die gelijk was aan het kleinst waarneembare verschil van 5 punten. De toename van schade van jaar 1-8 in de patiënten in de top 10% van toename van schade in jaar 1 was groter: 15,5 punt. In tegenstelling tot in oudere RA cohorten is het functioneren in het BeSt cohort over de tijd niet achteruit gegaan. We kunnen niet voorspellen of en wanneer na langer vervolgen het verschil in functioneren tussen patiënten met en zonder RRP wel klinisch relevant zal worden. Het afkappunt van 5 punten in het eerste jaar is mogelijk te laag en zou in plaats daarvan rond de 10 punten moeten liggen.

REACTIE OP BEHANDELING

Antilichamen tegen gecitrullineerde eiwitten (ACPA)

ACPA worden geassocieerd met zowel, bij patiënten met vroege artritis, een verhoogd risico van het ontwikkelen van RA en, bij patiënten met RA, een ernstiger ziektebeloop. ACPA positieve patiënten in oudere cohorten hadden hogere ziekteactiviteit, meer disfunctioneren en meer gewrichtsschade. Het is niet bekend of ACPA geassocieerd zijn met de reactie op behandeling gericht op lage ziekteactiviteit. In hoofdstuk 5 werd de associatie tussen ACPA en reactie op de behandeling geëvalueerd in het BeSt cohort. We vonden geen verschillen in klinische resultaten voor ACPA positieve patiënten in vergelijking met ACPA negatieve patiënten, behalve dat meer ACPA negatieve dan ACPA positieve patiënten in staat waren om medicatievrije remissie te bereiken en te behouden. Hoewel de ziekteactiviteit in gelijke mate werd onderdrukt in ACPA positieve en ACPA negatieve patiënten, was ACPA positiviteit als patiënten werden behandeld met initiële monotherapie geassocieerd met meer toename van radiologische schade in 8 jaar. Deze resultaten geven aan dat ACPA positieve patiënten baat hebben bij initiële combinatietherapie. Het verschil in de associatie tussen veranderingen in ziekteactiviteit en gewrichtsschade suggereren dat sturen op nog lagere ziekteactiviteit (bijvoorbeeld remissie) bij ACPA positieve patiënten ook zou kunnen leiden tot betere resultaten. Ook kan het in het bijzonder de moeite waard zijn om toename van radiologische schade in ACPA positieve patiënten regelmatig te controleren en zo nodig de behandeling hier op aan te passen.

Body mass index en reactie op behandeling

Het is aangetoond dat patiënten met meer vetweefsel en dus een hoge BMI meer ontsteking vertonen. Het zou kunnen dat deze patiënten minder goed reageren op

ontstekingsremmende medicijnen dan patiënten met een normale BMI. Dit is inderdaad aangetoond in RA patiënten behandeld met TNF-remmers, maar het verschil in behandeleffect tussen patiënten met een hoge en een normale BMI is misschien niet specifiek voor TNF-remmers. In hoofdstuk 6 onderzochten we de associatie tussen BMI en reactie op de behandeling in alle behandelgroepen van het BeSt cohort. We zagen dat patiënten met een hoge BMI een hoger risico hebben van onvoldoende reageren op initiële combinatietherapie met ofwel TNF-remmer infliximab of met prednison. Bij patiënten die behandeld werden met infliximab nadat zij op andere middelen gefaald hadden vonden we vergelijkbare resultaten. Het feit dat er geen verhoogd risico op onvoldoende respons op initiële monotherapie werd gevonden, kan verklaard worden door het feit dat veel patiënten onvoldoende reageerden op deze strategie, waardoor het moeilijker is om de rol van individuele risicofactoren te bestuderen. Onze hypothese was dat de verminderde reactie op behandeling zou worden veroorzaakt door cytokines geproduceerd door vetweefsel, maar we vonden geen tekenen en symptomen van verhoogde ontsteking bij patiënten met een hoge BMI. In plaats daarvan hadden patiënten met een hoge BMI hogere pijnscores en beoordeelden zij hun algemene gezondheid slechter. Een eventueel verschil in pijnrespons tussen patiënten met hoge en normale BMI, zoals eerder aangetoond in andere studies, kan tenminste een deel van het verschil in reactie op behandeling verklaren. Dit is van belang voor de klinische praktijk, aangezien een verandering van ontstekingsremmende medicatie niet nuttig zou zijn voor patiënten die kennelijk hoge ziekteactiviteit hebben door pijn geassocieerd met hoge BMI. Onze resultaten moeten worden bevestigd in een cohort dat ook gegevens over cytokines beschikbaar heeft om deze hypothese verder te onderbouwen.

STOPPEN VAN MEDICATIE

Infliximab

Initiële combinatietherapie met infliximab resulteerde in eerdere verbetering van ziekteactiviteit en functioneren en minder toename van radiologische schade in de eerste jaren van de ziekte. Aangezien TNF-remmers hoge kosten met zich meebrengen en geassocieerd zijn met een verhoogd risico van ernstige infecties, zou het goed zijn wanneer deze kunnen worden gestopt als het behandeldoel bereikt is. Eerdere studies hebben aangetoond dat dit inderdaad mogelijk is in sommige patiënten, maar in andere patiënten neemt de ziekteactiviteit toe na het stoppen. Herstarten van de medicatie zou kunnen leiden tot allergische reacties en het opnieuw bereiken van lage ziekteactiviteit of remissie kan enige tijd duren, of misschien niet in alle patiënten gebeuren. In hoofdstuk 7 hebben we gekeken naar de mogelijkheid van stoppen van initiële en verlate behandeling met infliximab in de BeSt studie en naar voorspellers van succesvol stoppen.

Stoppen na het bereiken van lage ziekteactiviteit gedurende ten minste 6 maanden kon in 45% van de patiënten die behandeld werden met infliximab. In 80% van de patiënten bleef de ziekteactiviteit laag gedurende ten minste 1 jaar na stoppen. Na een mediane follow-up duur van 7,2 jaar had 52% nog steeds lage ziekteactiviteit zonder infliximab te herstarten. Deze resultaten zouden een overschatting van het succes van infliximab staken in de dagelijkse praktijk kunnen zijn, aangezien in de dagelijkse praktijk het gebruik van TNF-remmers bijna beperkt is tot gebruik bij patiënten die eerder niet reageerden op methotrexaat en ten minste één andere synthetische DMARD. Patiënten die in de BeSt studie 'verlaat infliximab' ontvingen konden minder vaak stoppen met infliximab dan patiënten die infliximab als eerste behandeling kregen en ze hadden vaker opvlamming van de ziekteactiviteit na staken van infliximab, terwijl ze korter vervolgd werden na stoppen.

Herstarters bereikten meestal opnieuw lage ziekteactiviteit en infusiereacties kwamen niet vaker voor dan bij patiënten die voor het eerst met infliximab werden behandeld. Roken, de aanwezigheid van 'HLA shared epitope' (SE) en een behandelduur van ten minste 18 maanden waren voorspellend voor het opvlammen van ziekteactiviteit na het staken van infliximab, ook nadat behandeltiming aan het model werd toegevoegd. Hoewel ACPA positiviteit geen onafhankelijke voorspeller was, leverde het vervangen van SE met ACPA vergelijkbare resultaten op bij patiënten zonder risicofactoren, waardoor het model bruikbaarder werd voor de klinische praktijk. Het aantal patiënten dat na een jaar nog steeds gestopt was, was iets hoger dan in eerdere studies. Dit kan worden verklaard door de verschillen in de onderzochte patiënten: in de meeste andere studies hadden patiënten een langere ziekteduur en de meeste hadden gefaald op eerdere behandeling, terwijl in het BeSt cohort patiënten infliximab ook als initiële behandeling konden krijgen. Een andere mogelijke verklaring is dat de patiënten in onze studie door werden behandeld met methotrexaat na het staken van infliximab. In tegenstelling tot de meeste patiënten buiten een klinische studie werden de patiënten in de BeSt studie voor het starten van de behandeling geïnformeerd over het beleid om TNF-remmers te stoppen zodra lage ziekteactiviteit was bereikt. Ongeacht of infliximab opnieuw gestart moest worden na een opvlamming van de ziekteactiviteit, was toename van radiologische schade zeldzaam in het jaar na stoppen en het functioneren was stabiel in jaar 1 en 3 na stoppen. Er was echter een toename van disfunctioneren 5 jaar na stoppen van infliximab in vergelijking met functioneren op het moment van stoppen in patiënten die infliximab hadden herstart na een opvlamming van ziekteactiviteit. Dit kan echter ook een weerspiegeling zijn van de selectie van patiënten met een ernstiger ziektebeeld, in plaats van een effect van het stopzetten en herintroduceren van infliximab. Over het geheel genomen is het staken van TNF-remmers veilig en het heeft goede korte termijn resultaten, dus het kan worden geprobeerd, met name in niet-rokende, ACPA negatieve patiënten die snel op de behandeling hebben gereageerd.

Biologische anti-reumatische middelen

In hoofdstuk 8 hebben we een aantal studies beschreven die in het protocol staken van biologische middelen nadat het behandeldoel van lage ziekteactiviteit of remissie bereikt was, hadden opgenomen. Verlies van remissie of lage ziekteactiviteit na staken van biologische middelen werd bij 3% tot iets meer dan 50% van de patiënten gerapporteerd tijdens een follow-up duur variërend van 3 maanden tot meer dan 7 jaar. Op groepsniveau was er geen significante toename van gewrichtsschade in het jaar na stoppen. Eén studie vond een klinisch relevant verschil in functioneren tussen patiënten die in het eerste jaar een opvlamming van ziekteactiviteit hadden na stoppen en patiënten die dat niet hadden, maar drie andere studies vonden geen verslechtering van functioneren. Herbehandeling was succesvol in 75 tot 100 % van de patiënten. Milde infusiereacties kwamen voor in een aantal patiënten, maar dit aantal was niet hoger dan tijdens de eerste behandeling. In één studie werden antilichamen tegen medicatie bepaald en gevonden in 10% van de patiënten, vergeleken met geen van de patiënten die niet waren gestopt met biologische middelen, maar er werden geen klinische gevolgen van deze antilichamen gerapporteerd. De huidige richtlijnen voor de behandeling van patiënten met RA suggereren dat bij sommige patiënten biologische middelen kunnen worden stopgezet, maar geven geen evidence based advies over wanneer en in welke patiënten. De beschreven studies laten zien dat (tijdelijke) stopzetting mogelijk is in ten minste 50% van de patiënten. Patiënten moeten regelmatig worden gecontroleerd na het staken van de behandeling, zodat de behandeling kan worden hervat als de ziekteactiviteit toeneemt, en/of bij toename van gewrichtsschade. Patiënten met langdurige ziekte en patiënten buiten klinische studies waarin staken van medicatie aangekondigd was en onderdeel van het behandelprotocol, zouden in het bijzonder terughoudend kunnen zijn om hun biologische middel te staken, als dit effectief was in het verlagen van hun ziekteactiviteit, soms voor het eerst sinds hun diagnose. Lage verwachtingen van succes kunnen invloed hebben op de resultaten na staken van de behandeling. Dit kan met name relevant zijn in landen waar biologische middelen alleen kunnen worden gegeven aan patiënten die niet op synthetische DMARDs hebben gereageerd. Verwachtingsmanagement kan daarom een belangrijke rol spelen in de strategieën voor behandeling en staken van medicatie.

Medicatievrije remissie

In hoofdstuk 9 geven we een overzicht van recente studies die beëindiging van de laatste DMARD bij patiënten die in remissie zijn beschrijven: drie klinische studies en twee cohort studies. Tussen de 10 en 23% van de patiënten was in staat om alle DMARDs te staken, met lagere percentages in de cohort studies dan in de klinische studies. Ongeveer 45% van de patiënten moest medicatie na een opvlamming van ziekteactiviteit opnieuw starten, maar functioneren en toename van radiologische schade was

in deze patiënten hetzelfde als in patiënten met aanhoudende medicatievrije remissie. Eén van de twee studies waarin dit gerapporteerd is vond wel hogere ziekteactiviteit in herstarters, maar in de DAS-gestuurde BeSt studie behaalde de meerderheid van de patiënten weer remissie of op zijn minst lage ziekteactiviteit kort na herintroductie van hun DMARD. RF, ACPA en SE negativiteit en korte symptoomduur voor start van de behandeling waren onafhankelijke voorspellers van succesvol staken van medicatie. Omdat staken en herintroductie van DMARDs goede klinische en structurele resultaten oplevert op de korte termijn, betekent het feit dat patiënten met deze risicofactoren vaker moeten herstarten na het bereiken van medicatievrije remissie niet dat het stoppen niet kan worden geprobeerd. De voordelen van een periode zonder medicijnen kunnen opwegen tegen de mogelijke nadelen van een opvlamming van ziekteactiviteit. Verder onderzoek moet uitwijzen of verbeteringen in behandelstrategieën, zoals nog eerder in het ziekteverloop beginnen met de behandeling en initiële combinatietherapie, kunnen leiden tot nog hogere medicatievrije remissie percentages met goede klinische en structurele resultaten op de lange termijn.

GEZONDHEIDSGERELATEERDE KWALITEIT VAN LEVEN

Het is aangetoond dat gezondheidsgerelateerde kwaliteit van leven verbetert met de behandeling van RA. De huidige richtlijnen adviseren om de behandeling te sturen op remissie danwel lage ziekteactiviteit. Het is onbekend of remissie geassocieerd is met betere gezondheidsgerelateerde kwaliteit van leven dan lage ziekteactiviteit. In hoofdstuk 10 vonden we dat patiënten die in remissie waren inderdaad betere kwaliteit van leven hadden dan patiënten met lage ziekteactiviteit en dat een toename van de DAS gepaard ging met een verslechtering van kwaliteit van leven, ongeacht de vorige DAS. Patiënten die al lage ziekteactiviteit hadden en remissie bereikten, vertoonden een verbetering van hun kwaliteit van leven ten opzichte van patiënten die in lage ziekteactiviteit bleven. Deze bevindingen suggereren dat remissie naast met beter functioneren en minder toename van radiologische schade, ook geassocieerd is met betere kwaliteit van leven. Het zou echter ook zo kunnen zijn dat er patiëntkenmerken zijn die ervoor zorgen dat sommige patiënten remissie bereiken waar andere lage ziekteactiviteit behouden, waar we geen rekening mee hebben kunnen houden in onze analyses. Verder onderzoek moet uitwijzen of het bereiken van remissie inderdaad een verbetering van kwaliteit van leven *veroorzaakt*.

UITDAGINGEN VOOR DE TOEKOMST

Op groepsniveau hebben de introductie van vroege behandeling, combinatietherapie en behandeling met een vooraf bepaald behandeldoel geleid tot een aanzienlijke verbetering van de korte en middellange termijn uitkomsten van patiënten met reumatoïde artritis. Dit proefschrift heeft echter aangetoond dat er nog steeds ruimte voor verbetering en toekomstig onderzoek is op een aantal gebieden in de behandeling van vroege RA.

Er is nog steeds een relatief groot aantal patiënten met grote gewrichtsschade, wat onomkeerbaar disfunctioneren kan veroorzaken, hoewel de mate van schade minder is dan bij oudere cohorten na een vergelijkbare follow-up periode. Aangezien plaatselijke synovitis geassocieerd is met latere plaatselijke schade, kan onderzoek gericht op de rol van de lokale behandeling in grote gewrichtsschade een nieuwe therapeutische optie bieden om grote gewrichtsschade te voorkomen. Ten tweede moet onderzoek zich richten op die patiënten die aanzienlijke toename van radiologische schade hebben in het eerste jaar van de behandeling (snelle radiologische progressie, of RRP), ondanks behandeling gericht op het bereiken van lage ziekteactiviteit. Het feit dat het al aanwezig zijn van radiologische schade als de diagnose gesteld wordt, geassocieerd is met RRP zou er op kunnen wijzen dat de behandeling al eerder in het ziekteverloop moet worden gestart bij deze patiënten. De nieuwe RA criteria kunnen worden gebruikt om patiënten voor klinische onderzoeken te selecteren om de voordelen van het eerder starten van de behandeling in deze subpopulatie evalueren. Aan de andere kant zou de aanwezigheid van gewrichtsschade vóór aanvang van de behandeling ook een marker kunnen zijn voor het hebben van risicofactoren voor verdere gewrichtsschade. In dat geval zouden deze patiënten baat hebben bij het instellen van een strikter behandeldoel. Dit wordt ook gesuggereerd door het feit dat de aanwezigheid van ACPA, een van de risicofactoren voor RRP, is geassocieerd met meer toename van gewrichtsschade per punt van de DAS. Meer onderzoek is nodig om de hypothese dat een strikter behandeldoel gunstig is voor deze hoog risico patiënten, en mogelijk voor alle RA patiënten, te ondersteunen, zoals wordt gesuggereerd in de EULAR richtlijnen. Intuïtief zou het uiteindelijke doel van de behandeling remissie in alle RA patiënten zijn, maar het is nooit bewezen dat behandeling *gericht op* remissie zal leiden tot betere klinische, structurele en patiënt gerapporteerde uitkomsten bij alle patiënten dan behandeling gericht op lage ziekteactiviteit. Onnodige aanpassingen van de behandeling en het gebruik van te veel antireumatische geneesmiddelen kunnen de keerzijde van een dergelijke remissie gerichte behandelstrategie zijn, met hoge kosten, mogelijke bijwerkingen, onvervulde verwachtingen en uiteindelijk slechtere resultaten. Een gerandomiseerde trial ter vergelijking van het streven naar lage ziekteactiviteit en remissie, met blok randomisatie voor autoantilichaamstatus, zodat een gestratificeerde analyse kan worden verricht, kan

antwoord geven op de vraag of het streven naar remissie inderdaad superieur is aan het streven naar lage ziekteactiviteit.

CONCLUSIE

Dit proefschrift toont aan dat aanhoudend lage ziekteactiviteit gestuurd behandelen mogelijk is en leidt tot het behoud van goed functioneren in de meerderheid van de patiënten gedurende 8 jaar follow-up. Patiënten met schade aan de grote gewrichten en/of snelle toename van radiologische schade hadden iets hogere ziekteactiviteit gedurende 8 jaar follow-up dan patiënten die dat niet hadden. Dit geeft aan dat adequate ziektebestrijding een belangrijke rol speelt bij het behoud van functioneren. Een manier om dit te bereiken is om vroeg in het ziektebeloop met combinatietherapie te starten. De potentiële nadelen; een verhoogd risico op bijwerkingen en hoge kosten, kunnen worden geminimaliseerd door medicatie af te bouwen zodra het behandeldoel bereikt is gedurende een periode van ongeveer 6 maanden. Met behulp van bekende voorspellers van het ziekteverloop en reactie op medicatie en het zoeken naar nieuwe (bio) markers, kan de behandeling verder worden aangepast om te voorkomen dat effectieve behandeling wordt onthouden totdat andere strategieën zonder succes geprobeerd zijn, en anderzijds overbehandeling te voorkomen. Een andere belangrijke stap in de richting van het personaliseren van de behandeling van RA is het verder ontrafelen van de pathogenese van ACPA positieve en ACPA negatieve ziekte. Het zou kunnen dat deze verschillend is, en dat ACPA positieve en ACPA negatieve ziekte daarom verschillende behandelstrategieën vereisen, zoals wordt gesuggereerd door het verschil in gewrichtsschade bij ACPA positieve patiënten die aanvankelijk werden behandeld met monotherapie. Uiteindelijk moet vroege gepersonaliseerde behandeling met een vooraf vastgesteld behandeldoel leiden tot snelle onderdrukking van ziekteactiviteit, zodat daarna medicatie kan worden afgebouwd, terwijl goed functioneren en gewrichtskwaliteit behouden blijven in alle RA patiënten.

Appendix

ROLE OF THE FUNDING SOURCE

The rheumatologists participating in the Foundation for Applied Rheumatology Research were responsible for the study design and data collection in the BeSt study. The authors are responsible for the data analysis, interpretation of all data, writing the manuscripts and the decision to publish. The BeSt study was supported by the Dutch College for Health Insurances with additional funding by Janssen Biologics B.V. and Schering Plough B.V., but did not participate in other activities.

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CURRICULUM VITAE

Marianne is geboren op 7 februari 1984 in Nieuw-Vennep. Na het behalen van haar tweetalig gymnasiumdiploma aan het Rijnland Lyceum in Oegstgeest begon zij in 2001 met de studie biomedische wetenschappen aan de Universiteit van Leiden. Na het behalen van haar propedeuse stapte zij in 2002 over naar de studie geneeskunde in Leiden. In 2009 legde zij het artsexamen af, waarna zij kort als arts-assistent interne geneeskunde in het Bronovo Ziekenhuis in Den Haag heeft gewerkt.

Vanaf februari 2010 was zij verbonden als arts-onderzoekster aan de afdeling reumatologie van het Leids Universitair Medisch Centrum. Onder begeleiding van mw. dr. C.F. Allaart, prof. dr. T.W.J. Huizinga, prof. dr. W.F. Lems en dr. P.J.S.M. Kerstens werkte zij aan het onderzoek beschreven in dit proefschrift. In 2012 combineerde zij deze taak gedurende een half jaar met een klinische stage op de afdeling ambulante zorg van de reumatologie onder begeleiding van dr. C.F. Allaart.

Sinds 1 mei 2013 is zij werkzaam als arts-assistent psychiatrie bij Rivierduinen, Leiden.

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