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**Author:** Broek, Marianne van den  
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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. 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. Prolonged inflammation is associated with extra-articular disease and co-morbidity such as cardiovascular disease.

In 1987, classification criteria were developed to separate rheumatoid arthritis from other inflammatory disorders. 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.

### ACR 1987 criteria
1. Morning stiffness (at least 1 h)
2. Arthritis of 3 or more joint areas
3. Arthritis of hand joints (≥1 swollen joints)
4. Symmetrical arthritis
5. Rheumatoid nodules
6. Serum rheumatoid factor
7. Radiographic changes (erosions)

Four or seven criteria must be present. Criteria 1-4 must have been present for at least 6 weeks.

### ACR/EULAR 2010 criteria
1. Joint involvement (0-5)
   - One medium-to-large joint (0)
   - Two to ten medium-to-large joints (1)
   - One to three small joints (large joints not counted) (2)
   - Four to ten small joints (large joints not counted) (3)
   - More than ten joints (at least 1 small joint) (5)
2. Serology (0-3)
   - Negative RF and negative ACPA (0)
   - Low positive RF or low positive ACPA (2)
   - High positive RF or high positive ACPA (3)
3. Acute phase reactants (0-1)
   - Normal CRP and normal ESR (0)
   - Abnormal CRP or abnormal ESR (1)
4. Duration of symptoms (0-1)
   - Less than 6 weeks (0)
   - 6 weeks or more (1)

Cutpoint for rheumatoid arthritis 6 points or more, or having a) typical erosions, or b) long-standing disease previously satisfying the criteria.

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. 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. Citrulline is generated by post-translational modification of arginine by peptidylarginine deaminase. ACPA can be found years before the diagnosis of RA is made. It has been suggested that ACPA play a role in both the process of developing RA as well as the chronicity of the disease. 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. 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. 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.

**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. Methotrexate is generally considered the anchor drug for the treatment of RA. 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. 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. Prolonged disease activity may in these patients be prevented if a biologic anti-rheumatic agent is introduced.
Chapter 1

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. It can be calculated using the following formula:

\[ \text{DAS} = 0.54 \sqrt{\text{RAI}} + 0.065 \times \text{SJC} + 0.33 \ln \text{ESR} + 0.072 \times \text{GH}. \]

Patients with a DAS higher than 2.4 are considered to have high disease activity. 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. It has been suggested that the goal of treatment should be even more stringent: remission. Remission can be defined as a DAS<1.6. 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. Both definitions have similar associations with functional ability and joint damage progression.

Functional ability
Functional ability is considered one of the most important patient reported outcomes in clinical trials. The health assessment questionnaire (HAQ) was designed to measure functional ability in RA patients. 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. A difference of around 0.2 is considered clinically significant. 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. 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). 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.\textsuperscript{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.\textsuperscript{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. 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, 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.

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. 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. 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. 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. 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. 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. 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 associ-
ated 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 biologi-
cal 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.


