Improving targeted treatment in early rheumatoid and undifferentiated arthritis

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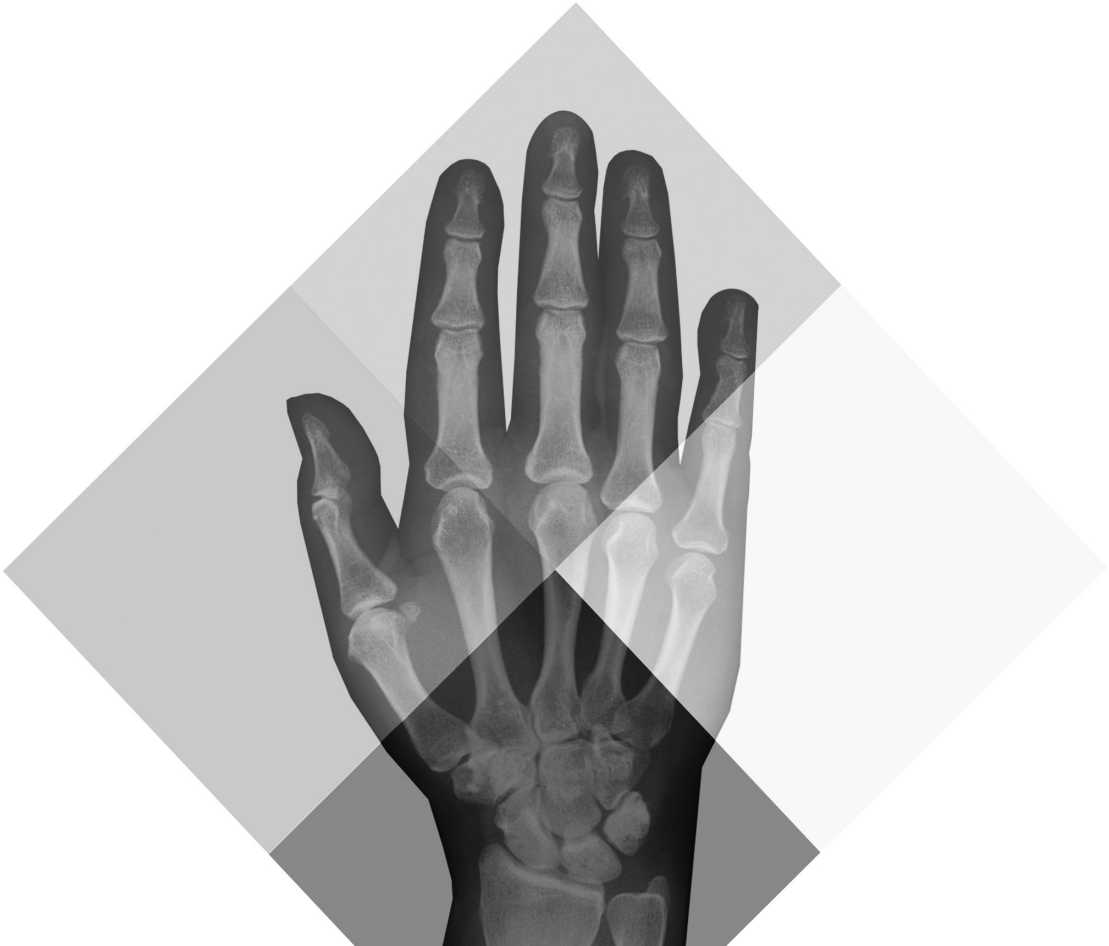
Chapter 10

SUMMARY AND CONCLUSION



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

THE IMPROVED STUDY

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

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

JOINT DAMAGE

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

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

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

INTRA-ARTICULAR INJECTIONS

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

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

ACPA-NEGATIVE RA

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

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

TREATMENT TARGET

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

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

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

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

FUTURE PERSPECTIVES AND CONCLUSION

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

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

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

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

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

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

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

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